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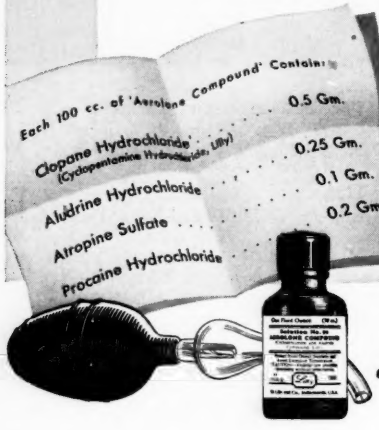
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REACTIONS OF TOXICITY INCIDENT TO ANTIBIOTIC THERAPY AND THEIR MANAGEMENT

WALLACE E. HERRELL, M.D., F.A.C.P.
Lexington, Kentucky

PENICILLIN

IT IS indeed fortunate that penicillin, the first antibiotic agent of great practical value, possesses little or no toxicity. The side effects of penicillin therapy are fairly well known to all. The most important toxic effect has to do with hypersensitivity, which usually manifests itself as a cutaneous reaction. It may take the form of a maculopapular type of rash or urticaria. While in many instances it is mild, it may on occasion be severe, and may be associated with varying degrees of arthralgia from mild joint pain to severe joint pain and swelling. It is well, further, to emphasize that the cutaneous as well as the joint manifestations of toxicity may occur many days after the use of penicillin has been discontinued. The control of these reactions is first of all a matter of discontinuing use of the antibiotic and using one of the antihistamines, such as tripelennamine hydrochloride (pyribenzamine), in amounts of 50 mg three times daily. In the problem of severe urticarial reactions with swollen, painful joints, the degree of which at times may approach that seen in serum sickness, one recent development warrants comment. Very dramatic improvement may occur in these patients after the administration of 100 mg of cortisone three times daily for one day or two days.

Another cutaneous manifestation of toxicity from penicillin therapy is the so-called *Id.* reaction. It is not uncommon for individuals who suffer from or who have previously had trichophytosis to experience a definite flare of this condition after they receive penicillin for other reasons. The reaction may be mild but at times may be quite severe, requiring special treatment.

In our experience, the incidence of cutaneous reactions of toxicity is

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highest after the oral use of penicillin, particularly after the use of troches which are held in the mouth. Next in order of frequency are those reactions which follow the use of aqueous penicillin; the lowest incidence of reactions occurs after the use of procaine penicillin. Stomatitis and nasopharyngitis of a very angry-looking nature may at times follow the oral use of penicillin, particularly in the form of troches, as just mentioned. This may be confused with a serious lesion of the throat. Such a condition poses a real problem to the clinician, who must decide whether to continue antibiotic therapy or to discontinue it. If one is aware of the possibility of this reaction, and if the patient is not ill in proportion to the appearance of the throat, it is by all means advisable to discontinue use of the agent.

The occurrence of drug fever after penicillin therapy is very common. On the other hand, it is well to remember that drug fever can occur when enormous doses of penicillin are administered. If, for example, one sees a patient with subacute bacterial endocarditis who is receiving 5,000,000 to 10,000,000 units or more of penicillin per day and if culture of specimens of blood gives negative results, the fever may well be due to penicillin. Even the purest penicillin may contain small amounts of some pyrogen which will produce fever when enormous doses are used. If one wishes to administer penicillin to a patient who is known to be sensitive to the agent, two procedures are open. First, one of the new hypo-allergic penicillins can be employed. On the other hand, patients may in time become sensitive to these forms. Second, the patient can be desensitized to penicillin, a procedure which we, on occasion, have used. To do this, the beginning doses are extremely small, in the order of 1,000 units of penicillin per day; they are gradually increased by 1,000 to 5,000 units, at which time the patient receives, in addition to penicillin, 50 mg of pyribenzamine three times daily. Fortunately, since the introduction of the newer antibiotics, this laborious procedure, which requires four weeks, is not often necessary. However, occasions may arise when desensitizing patients to penicillin may be necessary.

You are familiar with the occasional report of black tongue after penicillin therapy. This is of no practical significance. It is generally thought to be due to a deficiency of the vitamin B complex. If there is anything to be done about it, it would be merely to administer multiple vitamins. I am familiar with some reports to the effect that the use of penicillin may interfere with the coagulability of the blood. While minor variations in coagulability have been noted, depending upon the method of study used, it is my conviction that this matter is of no practical significance whatsoever.

There are a number of fatal reactions that have been attributed to the use of penicillin. I refer specifically to those instances in which such conditions as serious disturbances of the hemapoietic system, as well as periarteritis nodosa, have been attributed to the use of penicillin. It is my

conviction that the evidence presented does not conclusively show that penicillin was responsible for these reactions. The only fatal reactions for which the use of penicillin could have been responsible have been in the rare instances of death due to anaphylaxis. These reactions, for the most part, have occurred in patients with a strong allergic history and particularly in patients with a history of asthmatic bronchitis. Any physician who gives penicillin to patients with asthma and strong allergic histories will do well always to keep at hand adrenaline to be administered to the patient at the first sign of the development of any reaction suggestive of anaphylactic-like shock. Since these reactions occur within fifteen to thirty minutes after injection, it seems advisable that patients with any suggestion of an allergic or asthmatic background not be dismissed immediately after penicillin is injected.

STREPTOMYCIN

Cutaneous reactions may occur in patients who are receiving streptomycin, although the incidence of such reactions is not high. They may, similarly, take the form of a maculopapular type of rash or an urticarial reaction. The treatment or management is the same as that mentioned in the section on penicillin.

Toxicity involving the eighth cranial nerve is by far the most important reaction that may accompany or follow streptomycin therapy. On the other hand, much undue apprehension exists concerning possible damage to the eighth cranial nerve after streptomycin therapy. If the forms of streptomycin currently available are used, and if the clinician will concern himself with two other factors, namely, the dose and the matter of renal function, little distress need be envisaged.

The preparation of choice has been dihydrostreptomycin sulfate, which is dispensed in solution. No single dose should exceed 1 gm. However, there is no contraindication to the intramuscular administration of 1 gm every twelve hours for as long as twelve days, provided, first of all, that the patient has normal renal function. If the patient has impaired renal function, concentrations of the drug in the serum will increase to a point that will invite neurotoxicity. If renal impairment exists, the dose should simply be adjusted accordingly. In other words, 1 gm can be given safely by the intramuscular route every twelve hours for twelve to fourteen days. Likewise, 0.5 gm can be administered every twelve hours for four weeks, provided renal function is normal. I stress this point simply because it is often desirable to combine streptomycin with the other antibiotics in the treatment of a variety of infections other than tuberculosis. There is good evidence that combined therapy is essential in the successful treatment of many infections, such as brucellosis, bacteremia, meningitis and subacute bacterial endocarditis. As you also are aware, streptomycin is combined with para-aminosalicylic acid very effectively in the treatment of tuberculous lesions. Likewise, streptomycin has been successful combined with isoniazid in the treatment of tuberculosis and in some instances

all three of these preparations are given simultaneously in the treatment of this disease. There is some evidence to suggest that the use of a preparation which contains equal parts of streptomycin and dihydrostreptomycin is an effective method of reducing eighth nerve toxicity. However, even with this preparation, I am sure that it is important to check renal function in patients receiving the streptomycins, since impaired renal function will favor the development of high serum levels, even on a reduced dose schedule.

CHLORAMPHENICOL

Chloramphenicol is an important antibiotic, but it is my conviction that it has no advantage over either aureomycin or terramycin. Its use may be associated with less gastrointestinal irritation than is encountered when the other two broad-spectrum antibiotics are used; however, chloramphenicol should be used with extreme caution. I shall give my reasons for this statement. Chloramphenicol is not so active, weight for weight, against many microbes, as are terramycin and aureomycin. Large amounts of chloramphenicol are excreted in the bile and in the urine in a biologically inactive form. Finally and most important, a chloramphenicol is a synthetically prepared nitrophenol compound, and its use may be associated with suppression of the bone marrow. This suppression may take the form of leukopenia, but, more important, fatal aplastic anemia may result from use of the drug. Reports are rapidly appearing concerning cases of aplastic anemia with a fatal terminus in which there can be no doubt that chloramphenicol was the responsible factor. There are only a few circumstances in which chloramphenicol is used on our services. It is the drug of choice in the treatment of typhoid fever and paratyphoid infections. Occasionally it will inhibit a *Staphylococcus* which cannot be inhibited by penicillin, terramycin or aureomycin, and it is in this condition, namely, a staphylococcic sepsis, plus typhoid fever and paratyphoid fever, that we consider its use justified.

AUREOMYCIN AND TERRAMYCIN

I propose to discuss the toxic effects of these two antibiotics together, but not because they are identical compounds, for as a matter of fact, they are chemically different, although this difference is only slight. However, this slight difference in chemical structure is sufficient to render them different biologically speaking. The commonest and most troublesome problem which follows the use of either terramycin or aureomycin has had to do with gastrointestinal irritation, predominantly nausea and vomiting. The use of aluminum hydroxide gels is helpful in controlling nausea and vomiting; however, the gels interfere somewhat with absorption and in general should not be used. The incidence of nausea and vomiting after use of these two agents has been considerably reduced among patients since it has been our policy to administer aureomycin or terramycin with cold, pasteurized milk. The use of milk, however, may

be undesirable in the preoperative preparation of patients for whom a low-residue or non-residue diet is desired.

Furthermore, some individuals cannot tolerate milk. In such instances it has been found that sodium bicarbonate can be substituted for milk and that it will control the nausea. It does not interfere with absorption. The patient receives 5 grains of sodium bicarbonate for each 250-mg capsule of the antibiotic. It appears that the use of aureomycin calcium caseinate is associated with very little nausea and vomiting.

The prolonged use of terramycin or aureomycin, which brings about marked suppression of the bacterial flora of the intestine, may result in some evidence of vitamin deficiency. This can be combated simply by the daily administration of multiple vitamin preparations. A marked change in the bacterial flora of the mouths of patients receiving aureomycin or terramycin has been observed. The bacterial flora disappears and a fungous flora is established which usually consists of Monilia albicans. This may result in glossitis. The development of black tongue, such as has been reported to follow the use of penicillin, may occur after the use of aureomycin or terramycin. As I have already said, it is thought to represent a deficiency of the components of the vitamin B complex.

There has been much concern over the development of a fatal colitis following the use of terramycin or aureomycin in the preparation of patients for bowel operation. This colitis is due to strains of Micrococcus pyogenes which are resistant to terramycin and aureomycin. It should rarely, if ever, be fatal. When a patient develops diarrhea and evidence of shock during the postoperative period, smears of the stools and cultures should be obtained immediately. If Staphylococci are present, erythromycin therapy should be started at once. Within forty-eight to seventy-two hours the Staphylococci can be eliminated from the stools and the patient will recover.

Perirectal irritation and also vaginal irritation with pruritus are well recognized by those who have used either aureomycin or terramycin to any extent. In my experience, however, this is not a troublesome reaction in patients who receive short-term courses. Such irritation is more likely to occur among people who have received rather insignificant doses and have been allowed to take these antibiotics for a number of days or weeks. There are some who feel that this perirectal and vaginal irritation is a matter, again, of suppression of the normal bacterial flora, which in turn allows an overgrowth of Monilia albicans. I know of no highly effective method of dealing with the rectal irritation, other than to discontinue use of the medication promptly. The diet should contain buttermilk and protein in high quantity. Witchhazel packs applied locally at times are helpful. The local application of gentian violet around the rectum and vagina has been advocated by some to control the moniliasis.

To date, the incidence of cutaneous reactions after the administration of aureomycin and terramycin has been unusually low. Hundreds of patients have received these antibiotics, yet the literature contains only a few re-

ports of cutaneous reactions of toxicity. These reactions can occur, and may take the form of urticaria or rash. Withdrawal of the drug, as a rule, will be followed by disappearance of the rash. There are some reports that these antibiotics, like penicillin, interfere with the coagulability of the blood; but here again it is my conviction that this phenomenon is of no practical significance.

No serious toxic reactions have been encountered following the use of erythromycin. The only reaction of any significance has been in the nature of gastrointestinal complaints. If the dose of erythromycin is in excess of 300 mg every six hours, one may on occasion develop nausea and slight diarrhea. This can be controlled simply by regulating the dose of the antibiotic.

MISCELLANEOUS ANTIBIOTICS

Here I should like to consider some of the antibiotics, many of which for various reasons are not in widespread use.

Neomycin is an example. It is active against a number of microbes, including Mycobacterium tuberculosis. Serious reactions of toxicity can occur, however, after the systemic use of neomycin. The reactions include involvement of the eighth cranial nerve, as well as renal irritation. If this antibiotic is to be used, it should be used cautiously, to a very limited degree, and only when other antibiotics are ineffective. There is no objection to its use in the form of a solution or an ointment as a local agent in the treatment of certain infections.

Bacitracin is another antibiotic that has received some attention. It, too, can be used effectively as a local agent. The systemic use of bacitracin is justified only in those conditions in which the organism is found to be resistant to the safer antibiotics. The dose should be small and the condition of the patient should be followed with extreme care. Because of the tendency of bacitracin to produce renal irritation, careful studies of renal function are imperative when the drug is used. The dose never should exceed 10,000 units given intramuscularly four times a day.

Polymyxin (aerosporin) is still another antibiotic, the use of which may cause important reactions of toxicity. There is only one situation in which the systemic use of polymyxin should be seriously considered at present, and that is in the presence of infections caused by Pseudomonas aeruginosa. The daily dose should not exceed 100 to 200 mg given by the intramuscular route in four divided doses. The reactions of toxicity which may follow its use include severe pain at the site of injection. Furthermore, neurotoxic effects, such as paresthesias and cerebellar ataxia, may occur.

Finally, I make a plea for more intelligent use of the antibiotics and more regard on the part of the clinical investigators for their potential toxicity. It is most unfortunate that these lifesaving agents are used indiscriminately.

190 North Upper Street

THE INCIDENCE OF ALLERGY TO DRUGS IN PEDIATRIC PRACTICE

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CONSIDERATION in the pediatric literature to date of abnormal reactions to drugs has consisted only of isolated case reports or studies of individual medications and not the over-all incidence of disagreement to drugs in this age group. For purposes of this discussion, by drug "idiosyncrasy" is meant an abnormal *quantitative* response to a drug. For example, a small therapeutic dose of atropine as used to control sneezing in pollinosis may cause slight dryness of the nose and throat—its normal physiological reaction. If such a dose causes a generalized erythema, dilatation of the pupils and abdominal distention, this represents an abnormal quantitative reaction to the drug in the direction of its expected effect when administered in toxic doses. Another patient might conceivably be given, through error, a truly toxic dose of atropine and demonstrate only minimal physiologic reactions. This would represent idiosyncrasy in the direction of a decreased quantitative response to the drug.

By drug "allergy" is meant an abnormal *qualitative* response which has no relationship to the normal physiological reactions of the drug in any dosage, as for example, urticaria produced by penicillin. The term "hypersensitivity" when applied to a drug usually denotes "idiosyncrasy" as described above in the direction of an increased response to the physiological action of the drug.

Confusion arises because the terms "hypersensitivity" and "allergy" are so frequently used interchangeably. If one makes the statement that August-to-frost pollinosis is due to allergy to ragweed pollen or that it is due to hypersensitivity to ragweed pollen, there is no confusion as to what is meant. However, in speaking of drugs one must be more precise and the definitions given above are at least appropriate to this discussion. It is possible that drug idiosyncrasy may be in some way related to drug allergy since, in a sense, it represents a state of altered reactivity, but just what this relationship may be is at present unknown.

It was the purpose of this study to determine the frequency of usage of various common medications as well as the incidence of adverse reactions to them in pediatric practice. The adverse reactions observed by us

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Dr. Berkowitz is Visiting Fellow in Pediatric Allergy.
Dr. Johnstone is a Fellow in Pediatric Allergy.

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TABLE I. LIST OF DRUGS MOST COMMONLY USED

	No. of Patients
1. Aspirin	450
2. Penicillin	411
3. Sulfonamides	292
4. Phenobarbital	260
5. Codeine	231
6. Aureomycin	208
7. Pyribenzamine	188
8. Ephedrine	141
9. Benadryl	140
10. Terramycin	112
11. Other antihistaminics	77
12. Aminophyllin	80
13. Epinephrine	75
14. Other sympathomimetics	80
15. Opiates other than codeine	68
16. Atropine	65
17. Sedatives other than phenobarbital	57
18. Chloromycetin	45
19. Iodine	32
20. Streptomycin	20

were practically all in the direction of drug allergy although it is quite possible that in a few instances the reaction represented idiosyncrasy. The relationship of "side reactions" of drugs to allergy will be discussed subsequently. Special attention was given to the relative incidence of drug intolerance in the allergic as compared to the non-allergic child.

When an untoward reaction did occur no attempt was made to determine if it were due to the active principle of the drug or to some excipient as we do not believe that this is a matter of great importance in the majority of instances.

When this study was started, we attempted to differentiate between the better known typical allergic reactions to drugs as rashes of various types, angioedema, asthma, rhinitis and pruritus and what we grouped as "side reaction," because there could be some question as to whether or not these represented true allergic responses to the drugs. In a young child, for example, nausea and vomiting following a drug may be merely an expression of the patient's resentment toward being compelled to take any type of medication. Other "side reactions" may be due to infection and not to the drug administered. These included ataxia, abdominal distress, bladder discomfort, depression, diarrhea, dizziness, drowsiness, excitement, fever, headache, hematuria, irritability, joint pains, stomatitis and others. However, as will subsequently be shown, these so-called "side reactions" occurred so much more commonly in the allergic than in the non-allergic children that in most instances they probably represent allergic reactions, or the altered reaction of the allergic individual to disease. We might perhaps better have used the term, "minor drug allergies" than "side reactions."

METHODS

Special questionnaires were prepared to record whether or not a given child had ever been treated with certain drugs. The mother of each child was carefully questioned concerning adverse reactions of the child to these

TABLE II. PERCENTAGE INCIDENCE OF ALLERGIC AND "SIDE EFFECTS" TO DRUGS IN ALLERGIC AND NON-ALLERGIC CHILDREN

	Incidence of Allergic Reactions			Incidence of "Side-Reactions"		
	In Allergic Children	In Non-Allergic Children	Overall Incidence	In Allergic Children	In Non-Allergic Children	Overall Incidence
Penicillin	10.0	—	6.8	2.1	—	1.4
Sulfonamides	6.7	4.7	6.1	7.7	2.3	6.2
Aureomycin	3.7	—	3.3	17.2	—	14.0
Terramycin	3.4	—	2.6	10.2	8.3	9.8
Benadryl	2.2	—	2.1	11.3	—	10.7
Atropin	2.0	—	1.5	8.3	—	6.2
Aspirin	1.9	—	1.3	2.3	0.7	1.7
Pyribenzamine	1.7	—	1.6	14.2	—	13.3
Codeine	1.5	—	1.3	3.6	—	3.0
Phenobarbital	—	—	—	13.0	1.5	9.6
Ephedrine	—	—	—	7.3	—	6.3
Aminophyllin	—	—	—	11.5	—	11.2
Epinephrine	—	—	—	3.0	—	2.6
Totals	20.0	2.4	12.8	36.0	3.5	25.0

drugs. Unless she was certain both as to the fact that her child had been given a certain drug as well as to whether he had reacted unfavorably to it, the particular drug was not checked off on the questionnaire as having been given. In addition each mother was carefully questioned as to the incidence of allergic disease in her child. Using these forms, drug histories were obtained on patients seen in the private practice of a pediatric allergist as well as in the general pediatric out-patient clinic of the Rochester General Hospital. This study included 500 infants and children ranging in age from two months to fifteen years. These patients were unselected, being taken successively as they came to either the office or the clinic over a five-month period. Of these patients 280 were boys and 220 were girls. Three hundred and thirty-two (66.4 per cent) of the 500 children had a history of allergic disease. The remaining 168 chidren (33.6 per cent) had no history of allergic disease and for the purposes of this study were considered as "non-allergic" children.

RESULTS

Table I shows the frequency of usage of the twenty most commonly employed drugs. It is an interesting commentary on present-day methods of treatment that penicillin is used almost as freely as aspirin, and these are the two drugs most commonly used in pediatric practice. Table II shows the incidence of drug reactions, both allergic and those grouped as "side reactions." Twenty per cent of the allergic group gave allergic reactions to drugs as compared to 2.4 per cent of the non-allergic group. "Side reactions" occurred in 36 per cent of allergic children as compared to 3.5 per cent of the non-allergic children. The overall incidence of drug allergy for the whole group of 500 children (exclusive of "side reactions") was 12.2 per cent.

Penicillin was administered to 411 children, of whom 280 were known to be allergic. The route of administration was not recorded. Of the

allergic children who received this drug, 10 per cent developed reactions. No allergic reactions occurred in the non-allergic children. The overall incidence of an allergic response to penicillin was 6.8 per cent. The allergic reactions encountered were: urticaria or angioedema in fourteen children, morbilliform eruptions in eleven and atopic dermatitis in two. Classified as "side reactions" were vomiting, diarrhea and joint pains, each of which occurred in one child, and local swelling and pruritus at the site of injection in another child. These could well have been allergic reactions as they occurred only in allergic children.

Aureomycin was given 208 children, of whom 168 were allergic. Seven (3.7 per cent) had allergic reactions to this drug. No allergic reactions occurred in the non-allergic children. The overall reaction rate for the whole group was 3.3 per cent. The allergic reactions consisted of maculopapular eruptions in three children, urticaria in three children, aggravation of a previously existing atopic dermatitis in one child, and a contact dermatitis from the use of an ointment in one child. "Side reactions" occurred in 17.2 per cent of the allergic children and none occurred in the non-allergic group. The overall incidence of "side reactions" was 14 per cent. These consisted of gastric distress, nausea, vomiting and diarrhea.

Terramycin was given to 112 children, of whom eighty-eight were allergic. Allergic reactions occurred in three of the allergic children (3.4 per cent) and in none of the non-allergic. The allergic reactions were angioedema, a generalized morbilliform eruption, and erythema and desquamation in one child each. "Side reactions" similar to those occurring with aureomycin occurred in 10.2 per cent of the allergic children and this antibiotic, unlike penicillin and aureomycin, caused "side reactions" in non-allergic children (8.3 per cent) giving a total overall incidence of such reactions for this group of 9.8 per cent.

Various types of sulfonamide drugs were given to 292 children, of whom 207 were allergic. The incidence of allergic reactions in this group was 6.7 per cent for the allergic children and 4.7 per cent for the non-allergic group, with an overall incidence of 6.1 per cent. The allergic reactions consisted of erythematous and maculopapular rashes in seven children, urticaria in six, atopic dermatitis in three, asthma in one and pruritus in one. Classified as "side reactions" were nausea, fever, vomiting, hematuria, urinary discomfort, stomatitis and loose stools which occurred in 7.7 per cent of the allergic and 2.3 per cent of the non-allergic children for an overall incidence of 6.2 per cent.

Benadryl was given to 140 children, of whom 138 were allergic. Three allergic children (2.3 per cent) developed allergic reactions, with one case each of pruritus, exacerbation of asthma, and exacerbation of atopic dermatitis. "Side reactions" consisting chiefly of feeling of drowsiness, vertigo, depression, irritability, nausea, vomiting, headache, ataxia and discomfort on urination, occurred in 11.3 per cent of the allergic children. No "side reactions" occurred in the seven non-allergic children receiving this

drug. In the few instances where the antihistaminics were used in non-allergic children, they were used chiefly as antipruritics.

Pyribenzamine was given to 188 children of whom 176 were allergic. Three allergic children (1.7 per cent) gave allergic reactions, with one case each of rhinitis, asthma and contact dermatitis from pyribenzamine ointment. "Side reactions" similar to those described for benadryl occurred in 14.2 per cent of the allergic children. No such reactions occurred in the twelve non-allergic children.

Aspirin, the drug most commonly used in pediatric practice, was taken by 450 children of whom 306 were allergic. Six (1.9 per cent) developed allergic reactions to this drug. No allergic reactions occurred in the 144 non-allergic children. The allergic reactions to aspirin consisted of urticaria in two children, asthma in two children, angioedema in one child and a morbilliform eruption on one child. Eight children (2.3 per cent) developed drowsiness or abdominal discomfort from aspirin. These were classified as "side reaction."

Codeine was given to 231 children, of whom 191 were allergic. Three of the allergic individuals (1.5 per cent) developed allergic reactions, two urticaria and one a generalized morbilliform rash. "Side reactions" such as nausea, vomiting, restlessness, gastric distress and excitement occurred in seven (3.6 per cent) of the allergic group; no reactions occurred in the forty non-allergic children.

Phenobarbital was used by 260 of the children, of whom 183 were allergic. There were no allergic reactions to this drug. However, twenty-four (13.1 per cent) showed "side reactions." Twenty were excited by this ordinarily sedative drug, two had emesis, one nausea, and one a prolonged "hangover." Only one non-allergic individual had a "side reaction" and this was excitement.

Atropine was administered to sixty-five children, of whom forty-nine were allergic. One allergic child (2.0 per cent) developed a generalized rash. "Side reactions" such as abdominal pain, flushing or erythema occurred in four (8.3 per cent) of the allergic group.

No allergic reactions were reported from the following drugs in the group studied: aminophyllin, opiates other than codeine, antihistaminics other than pyribenzamine and benadryl, chloromycetin, ephedrine, epinephrine, iodine compounds, sedatives other than phenobarbital, and streptomycin. This, we are certain, is due to the small series as over the years we have seen allergic or "side reactions" to all of these drugs.

DISCUSSION

This presentation, because of the relatively small number of cases studied, does not pretend to be a definitive discussion of this subject. Nevertheless, it gives a fair picture of the drugs most commonly used in pediatric practice and the untoward reactions to them. These studies indicate a very definitely higher incidence of drug reactions in allergic as compared with

other non-allergic children, 20 per cent as compared with 2.4 per cent, an eightfold difference.

Of the thirteen drugs most used by the subjects of this study, the incidence of "side reactions" was in every case greater for the allergic children in the group than those with no previous history of allergic disease. We feel that in the case of phenobarbital and aureomycin this difference appeared significant. This indicates the very likely possibility, as mentioned in the introduction, that these side effects represent in most instances minor allergic reactions.

While we made no detailed studies of the age incidence of drug allergy in general, it seemed obvious to us that this was largely a function of age, due to the fact that the older the child the more likely he is to have received various types of medication.

SUMMARY

1. The incidence of abnormal reactions to drugs most commonly used by children was studied by interviewing the mothers of 500 children varying in age from two months to fifteen years.
2. The incidence of allergic drug reactions in allergic and non-allergic children is compared.
3. The incidence of what we have classified as "side reactions" to these drugs and their significance with respect to allergy is commented upon.
4. Tables are presented illustrating the above points of discussion.

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BRONCHIAL ASTHMA, SECONDARY TO CHRONIC PULMONARY MYCOSIS

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THE CLINICAL findings in mycotic infections of the lung are subject to considerable variation. The main course may be that of bronchitis, bronchopneumonia, indurative pneumonia or chronic pneumonitis with or without the formation of cavities. The similarity with lung tuberculosis may initially lead the diagnostician astray. Also, considering the vast number of non-pathogenic fungi and yeasts which may lodge in the oral cavity and upper respiratory tract or occur in the inhaled air, it is usually difficult if not impossible to make a diagnosis on the basis of sputum examinations without the assistance of an experienced mycologist. In order to evaluate the pathogenicity of fungi cultured from the patient's sputum one may have to resort to animal inoculation experiments; in some cases serologic or allergic reactions may prove to be of value.

Definitely known to be pathogenic are the *Aspergillus fumigatus* Fresenius and *A. Fischeri* Wehmer, *Sporotrichum Beurmanni* Matruchot et Ramon and the genera *Histoplasma, Blastomycoides, Coccidioides* and *Absidia.* Among the yeasts one should especially regard with suspicion the species *Torulopsis neoformans* (Sanfelice) Redaelli, *Candida albicans* (Robin) Berkhout, *Candida Tropicalis* (A. Castellani) Berkhout and *Trichosporon cutaneum* (de Beurmann, Gougerot et Vaucher) Ota. Guides to a correct diagnosis may further be found in the history, the absence of response to the usual therapeutic measurements, including antibiotic treatment, and the beneficial results obtained by specific antimycotic therapy.

While it is common knowledge that many airborne fungi may act as inhalation allergens in sensitized asthmatic patients, it would appear that the continued presence of pathogenic fungi in the respiratory tract, as found in mycotic lung infections, may itself become an internal source of allergens and cause asthma in previously non-asthmatic patients.

The following two patients as treated in our hospital are presented in order to demonstrate such a sequence. They illustrate certain aspects of the clinical findings, diagnosis and treatment. Their presentation is aimed at making the reader more on the alert for a possible diagnosis of pulmonary mycosis.

Case 1.—H., a fifty-seven-year-old farmer, was admitted to the hospital in February, 1949, with a diagnosis of asthma and chronic bronchitis. There were no known allergies in family. The history revealed daily attacks of shortness of breath usually in morning and evening. The first such attack occurred while

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harvesting rye in July, 1948. Previous to that time he never had respiratory complaints. Since then there had been a gradual aggravation of symptoms necessitating hospitalization elsewhere on two occasions each with diagnosis of asthma and chronic bronchitis. After the second hospital course there was rapid progressive deterioration of the general condition as evidenced by marked weight loss, in spite of normal appetite; increasing complaints of tiredness, dyspnea, tightness and frequent lancinating pains in the right chest.

At present admission H. appeared emaciated and exhausted, coughing continuously. Examination of the chest revealed a rigid thorax; lung bases low, hardly moving; percussion moderately suppressed in the right anterior lower half; on auscultation many moist and dry musical rhonchi, mainly expiratory and more so in the right lower chest; increased vascular markings and increased density in this area on x-ray together with bilateral enlargement of the hilar shadows. Skin reactions of the von Pirquet and Mantoux tests were negative. Hematologic findings: white blood court, 10,400; with 11 per cent eosinophiles and moderate shift to left; corrected sedimentation rate varying between 20 and 31 mm/one hour. Repeated sputum examinations remained negative for tubercle bacilli but revealed the presence of many eosinophiles and cells containing hemosiderin. The sputum contained an abundance of *Staphylococcus aureus* and some *Neisseriae catarrhales* together with fungal spores and an occasional mycelial thread.

While in an allergen-free observation room at the hospital the attacks of dyspnea decreased in intensity and frequency but tight sensations in chest and spells of coughing persisted unchanged. The temperature, normal in the morning, would rise to 100.8° F. in the evening. The patient's general condition was so poor at the time, that bronchograms and bronchoscopy were considered contraindicated; a malignant lung lesion could not definitely be ruled out.

Penicillin and fever therapy instituted initially, remained without results. It was observed that after a few days of penicillin treatment the temperature rose to 102.6° F.; simultaneously the patient complained of more severe pain in the right chest, while expectoration increased to 350 cc/twenty-four hours. The expectorated material was at first yellowish green and later of a reddish rusty color. Culture of this produced several hundred colonies of yeastlike growth (Difco wort agar).

Therapy was then changed to sulfathiazole and sulfadiazine in divided daily doses of 6 gm for five days. This resulted in a decreased amount of expectoration. The staphylococci disappeared completely after the third treatment. However, there was no change in fungus content nor was there any appreciable effect on the course of the patient's asthma; also, the blood picture remained about the same.

Meanwhile, we had prepared an allergenic extract from the isolated yeastlike fungus, which was classified as a new *Trichosporon* species. The patient gave a strongly positive skin reaction when tested intracutaneously with this extract. This finding, together with the other above mentioned observations, strongly suggested a diagnosis of mycotic infection involving the bronchi and limited areas of lung parenchyma and giving rise to asthmatic attacks as secondary manifestation.

The patient was thereupon given potassium iodide, up to 8 gm a day, and creosote, up to 1 gm a day. After one week his condition showed definite improvement, both subjectively and clinically. On sputum cultures the number of yeast colonies diminished conspicuously and only occasional yeast components could be detected in sputum smears. Following this the patient was given two intravenous injections of Neo-salvarsan, 150 mg on the first day, and 450 mg on the second day. Within two days all symptoms of asthma and bronchitis disappeared completely; the amount of sputum became reduced to 15 to 20 cc per twenty-four hours, and culture revealed only one yeast colony.

Neosalvarsan treatment was discontinued, however, because of unpleasant side reactions consisting of chills and moderate fever for several hours. Instead, patient was discharged from the hospital and treated as an outpatient with oral medication of potassium iodide 0.6 gm and creosote 0.3 gm a day.

During the following months the patient remained free of asthma. His weight improved steadily. Monthly check-ups of the sputum revealed nothing worth mentioning. His general condition has remained very satisfactory ever since, except for a two-week episode of bronchitis in May, 1950, not accompanied by asthma. The patient was last seen in August, 1952; he appeared physically normal, had no complaints; sputum was normal and the chest plate showed moderate fibrotic changes in the right middle and lower lung lobes.

Case 2.—A man, aged forty-two, who worked as an administrator, first seen in the clinic in December, 1949, with a complaint of recurrent asthma attacks for four years and a chronic cough since the age of seventeen years. The history revealed that this patient started working on a cucumber farm when fifteen years of age. The cucumbers were grown on fermented horse manure under artificial climatic conditions of high temperature and 100 per cent humidity. After having worked in this environment for a year and a half, he started coughing increasingly. This was diagnosed as due to chronic bronchitis, and the patient had to leave his work as a result of his ailment. The bronchitic manifestations persisted and failed to respond to any treatment during the following years. Although tubercle bacilli could never be demonstrated, tuberculosis was suspected and patient was under continuous observation by the Tuberculosis Consultation Bureau. At one time he took a rest for six months without beneficial result. Chest x-ray in July, 1943, showed increased hilar shadows and fibrotic changes radiating from the right hilus upward into the right apex, a homogeneous shadow of an infiltrative process occupying the upper part of the right lung. Chest x-ray in March, 1949, gave essentially the same picture. In October, 1949, the chest plate and tomograms showed for the first time small cavities in the right upper lung field with increased fibrosis, giving this area a honeycombed appearance.

Asthmatic complaints had started gradually in 1945 and had become more and more prominent in the course of the following years. Coughing and expectoration of moderate amounts of whitish sputum had remained unchanged.

When this tall thin man was first seen by us in December, 1949, there was percussion dullness in right upper chest with some coarse rhonchi in this area. Dry musical rhonchi and wheezing could be heard throughout the chest; normal temperature; white blood count varying between 9,800 and 15,000, with moderate eosinophilia; corrected sedimentation rate from 13 to 20 mm/one hour. Reactions of Pirquet and Mantoux tests were weekly positive. Allergic skin reactions were positive for house dust and for some ubiquitous *Penicillia and Mucorales;* also a markedly strong positive reaction to a mixture of ***Aspergillus*** species. Sputum culture gave a few non-pathogenic bacteria and many fungus colonies. The majority of the latter were identified as *Aspergillus Amstelodami* (Mangin) Thom et Church with a few colonies of *Aspergillus clavatus* Desmazieres; also one white colony of *Coniothyrium* species, a saprophyte usually found on dead twigs and leaves.

The various aspects of history, x-ray and laboratory findings suggested a diagnosis of primary mycotic disease with gradual development of allergy to the responsible fungus, manifested clinically as bronchial asthma.

Therapy was started with oral potassium iodide and creosote in moderate doses. No significant improvement resulted and sputum cultures kept producing a multitude of fungus colonies. The patient was thereupon treated with intravenous Neosalvarsan on three consecutive days: 150 mg, 300 mg and 450 mg. This resulted in con-

siderable subjective improvement; rhonchi and wheezing were diminished on auscultation; cultures during the following weeks produced only from five to twelve colonies of *Aspergillus Amstelodami.*

After several weeks a second course of intravenous Neosalvarsan was given on four consecutive days: 150 mg, 300 mg, 450 mg and again 450 mg. Since then sputum cultures have remained negative for fungi; the patient has had no more asthma attacks; within four months he gained fifteen pounds of weight; he only coughed occasionally, with minimal or no expectoration. Auscultation is clear except for some persistent dry coarse rhonchi in the right upper chest. X-ray on July 24, 1950, showed clearing of the infiltrative process with residual fibrotic changes and a few cavities still present. In October, 1952, he had no complaints.

COMMENT

In both cases presented here, there was a close parallelism between the number of fungus colonies and the asthmatic and bronchitic phenomena before and after treatment; skin reactions to extracts of the causative fungus were marked in each case; we therefore feel justified in concluding that these represent true examples of asthma secondary to the chronic presence of fungi in the respiratory tract.

The question arises of how the initial infection established itself. It is conceivable that in the first patient the infection was facilitated by inhalation of sharp dust particles from the rye, irritating the mucous membranes, or possibly a preceding staphylococcus aureus infection could have been the underlying factor. In the second case a tuberculous process may have preceded the mycosis, or possibly a congenital cystic condition may have been present, facilitating fungus infection in a highly contaminated atmospheric environment.

Treatment should, of course, be directed towards eradicating the causative fungus. In this respect the antibiotics and sulfa drugs appear to have been of no avail; in fact, in the first patient, the administration of penicillin may well have made the patient worse, as it was accompanied by an aggravation of symptoms. On the other hand, the Neosalvarsan therapy, so effective in both these patients, has given us equal satisfaction in the few other cases of bronchomycosis which we have treated since then. Intravenous Neosalvarsan, therefore, is probably the best treatment available at the present time.

SUMMARY

Two clinical case reviews are presented, in which the chronic presence of pathogenic fungi in the lung acted as the main etiologic factor in the development of bronchial asthma.

It is felt that among the many possible causes of intrinsic asthma and in cases of chronic bronchitis or indurative pneumonia, bronchomycoses and pneumonomycoses deserve more attention than they have hitherto received; they should be suspected especially in cases where eradication of bacterial factors has brought no improvement.

Treatment with intravenous Neosalvarsan has yielded excellent results in clearing the mycotic infection.

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ITALIAN SOCIETY OF ALLERGY

On June 15, at Florence, Italy, a new Board was elected: Prof. Virgilio Chini, Director of Institute of Medical Clinic, Bari University; Prof. Pietro Di Mattei, Director of Institute of Pharmacology, Rome University; Prof. Giovanni Favilli, Director of Institute of General Pathology, Bologna University; Prof. Franco Flarer, Director of Dermatological Clinic, Padova University; Prof. Antonio Iunedei, Director of Institute of Medical Pathology, Florence University; Prof. Guido Melli, Director of Institute of Medical Pathology, Milano University; Prof. Pietro Redaelli, Director of Institute of Pathology, Milano University; Prof. Piero Sangiorgi, Outside Teacher Milano University; Prof. Umberto Serafini, Assistant Professor of Medical Clinic, Rome University; Prof. Marcell Iusena, Director of Hospital, Milano; Prof. Flaviano Magrassi, Director Institute Medical Pathology of Napoli University.

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CLEANSING AGENTS—IRRITATING AND NON-IRRITATING TO THE SKIN

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SOAP IS the most valuable agent for the maintenance of cleanliness. It is universally used as a pleasant, efficient, harmless means of cleansing the skin. However, with some individuals and under certain conditions, soaps are irritating to the skin and initiate, aggravate or prolong its injury. Since personal and household sanitation have to be continued by these individuals the physician should know the composition and properties of soap, the irritant factors in soap and the appropriate methods of cleansing when the skin is "sensitive" to soap.

Composition of Soaps.—Soaps are chemical combinations of fatty acids and alkalies produced by the saponification of appropriate quantities of alkalies and animal or vegetable fats or their fatty acids. The alkalies used may be inorganic, such as the hydroxides of sodium, potassium and ammonium; or organic such as mono-, di- or triethanolamine.

The choice of alkali governs many of the physical characteristics of soap. Sodium hydroxide is the most widely used and its soaps are found in toilet bars as well as granulated and flaked household products. Potassium hydroxide is used principally in the manufacture of liquid soaps. Ammonium and triethanolamine soaps are primarily used in shampoos.

The quality of the soap manufactured is governed primarily by the nature of the fat or fats contained. Those commonly used are tallow, lanolin and the oils of cocoanut, corn, cottonseed, olive, palm, peanut, sesame, sunflower, linseed and soya.

Most of the commonly used toilet soap bars are not pure soaps. Essential oils as well as dyes and pigments are added to make a pleasantly perfumed and more attractive product. Substances such as rosin impart softness and produce a more soluble and a faster sudsing soap, particularly in cool water. Some soaps contain borax and abrasives—pumice, sand, talc and fibrous cellulose compounds for their mechanical "scrubbing" action. Numerous germicidal agents and many different drugs have been added for their medicinal value.

Soaps used for dishwashing, laundry and other household cleansing usually contain alkaline "builders" to increase their cleansing qualities. These may be sodium carbonate (soda ash), trisodium phosphate and pyrophosphates. Some household soaps also contain bleaching compounds for their value in the laundry.

Most soaps contain an appreciable amount of unsaturated fatty acids

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which are prone to become rancid or to discolor. Preservatives, usually sodium silicate, are added to prevent this discoloration.

Properties of Soap.—When soap is dissolved in water, it becomes ionized and partly hydrolyzed, with the formation of free alkali (usually sodium hydroxide). All aqueous soap solutions are, therefore, alkaline; including the so-called "neutral" toilet soaps which do not contain alkaline builders. The "built" household soaps usually are markedly alkaline even in low concentrations.

The detergent action of soap is not very well understood. However, it is common experience that soap not only removes "dirt" from the skin but also has a tendency to defat it. In order to overcome the alkalinity and defatting actions of soap, the so-called "superfatted" toilet bars are made with an excess of unsaponified fat. This excess fat is supposed to neutralize both the free alkali and the alkali which results from the hydrolysis of soap when in aqueous solution. This would be a desirable asset but has not proved to be possible and the excess fat increases the danger of rancidity.

Tap water contains calcium and magnesium salts. When these are in relatively high concentration the water is termed "hard." When soap dissolves in this water, it combines with the calcium and magnesium to form insoluble compounds—the "curd" or "ring around the tub." These salts also deposit on the skin and the clothing and are very difficult to rinse off.

Irritant Factors in Soap.—The surface layer of the skin is normally acid in reaction. This "acid mantle" is composed of the horny layer of the epithelium together with the products of excretion from the glands of the skin. The secretion of the sweat glands is definitely acid and contributes appreciably to the maintenance of the "acid mantle." The diminution of secretion of the sweat glands in cold weather, with a decrease in acidity of this protective layer has been given as one possible explanation of "winter itch." The "acid mantle" is essential to the health of the skin and helps to protect it from invasion by some pathogenic bacteria. The normal shingle-like arrangement of the horny layer of epidermis is of importance in protecting the body and in preventing penetration of injurious substances into the skin.

Pillsbury and Shaffer[7] have again shown that the surface layer of the skin is much more sensitive to alkalies than to acids. Blank[2] demonstrated that the normal pH of the surface layer of the skin ranges from 3.7 to 7.0 and that alkaline solutions are prone to produce cutaneous irritation. Klauder and Gross[6] found that the cutaneous pH of the hand ranged from 4.5 to 6.5. The lowest pH readings were found in hot humid days after perspiration.

Much of the irritation caused by soap has been ascribed to its alkalinity —primarily derived from its hydrolysis into free alkali, when in aqueous

solution. Simple washing of the hands with soap and water produced an elevation of the surface pH in the normal individual. This elevation of pH may persist for several hours. These investigators studied the pH of infant's skin after washing with soap and water and concluded that its defensive mechanism, in maintaining the normal pH, is even poorer than in the adult.

The alkalinity of soap solutions produces swelling of the horny layers of the epithelium as well as a partial debridement of this layer. In the majority of people, this disturbance of the protective layer is of no great significance. In those people who are abnormally sensitive, or where washing with soap and water is frequent, damage to the skin will result. The first indications of irritation are roughness and scaling. Finally, erythema and fissuring of the skin develops. The formation of fissures with oozing of serum further increases the alkalinity. Bernstein and Herrmann[1] again found the highest alkalinity and the most persistent pH raising effect of soap, present in the fissures in eczematous conditions.

In addition to the harmful effects of the alkalinity of soap, the possible sensitizing effect of added perfumes, builders, coloring agents, medications and added preservatives must be considered.

The irritation of the fatty acids in soap products has received considerable attention. Blank[2] found that fatty acids are potential eczematogenous agents. He felt that the fatty acids of low molecular weight such as those derived from cocoanut oil or palm kernel oil are more irritating than higher fatty acids. He also demonstrated that the fatty acids employed in making of soap are more irritating in alkaline solutions.

The Role of Soap in Cutaneous Irritation.—There are many reports in the literature of dermatitis apparently due to soaps.[11] Jordan, Dolce and Osborne[4] reported on 239 patients who had dermatitis of the hands in whom soap appeared to be the contributing cause. Guild[3] made a survey of 4,500 persons including physicians, dentists, nurses, students and lay people in order to determine the effect of soap as used in diverse occupations. Of this group 34 per cent gave a history indicating that soap had produced some dryness, scaling, itching, or burning of the skin.

It is usually contraindicated to use ordinary soaps in any eczematous process because of the irritating effects of the soap plus the increased alkalinity produced. There are many conditions of the skin in which the normal lubricants are already at a minimum. In these cases the degreasing effect of soap is certainly not beneficial.

The only solution to the problem of true soap dermatitis is the substitution of non-irritating cleansers which can be used for toilet and for general household and laundry cleansing.

The use of "castile" soap has been advocated for use in babies with a tender skin. Castile soaps were originally alkali saponification products of pure olive oil. Most of the castile soaps which are available today contain

large proportions of tallow soap or cocoanut oil soap. They may also contain the usual fillers and perfumes. It is therefore impossible to predict irritating or sensitizing properties of a particular castile soap unless the manufacturer supplies a complete formula.

A number of soap substitutes are offered physicians for use as skin cleansers when soap irritates. Some of these are merely superfatted soaps such as Basis,® Avaderma® and Stieffel's oilatum.®

Synthetic Detergents as Household Cleaners.—Since the end of the last war the domestic use of synthetic detergents (syndets) has shown a tremendous increase in proportion to the use of solid soap. In 1940 the comparative amount of "syndets" used was negligible. In 1950 syndets represented about 30 per cent of the combined soap and "syndet" market. In 1952 this increased to 40 per cent. The increase has been primarily in the household field. Synthetic detergents are surface-active organic compounds containing both hydrophilic and hydrophobic groups. There are three principal classes of "syndets," anionic, cationic and nonionic. The anionic class, to which soap itself belongs incidentally, is by far the most important. This class of compound ionizes in solution with the long-chain hydrophobic portion of the molecule included in the negatively-charged anion. The anionic detergents are the most commonly used cleansers today. The cationic surface-active compounds, which ionize to yield a positively-charged cation containing the elongated hydrophobic portion of the molecule, are generally poor detergents but powerful antiseptics. The nonionic detergents, nearly all of which are liquids, do not ionize in water. These compounds, many of which are good detergents, contain balanced hydrophobic and hydrophilic groups. They are used in some liquid household detergents and have many industrial applications.

The synthetic detergents have several advantages over soaps. They are approximately neutral in aqueous solutions. They will produce suds and therefore cleanse in alkaline, neutral or acid solutions. In addition they do not produce scums in hard water.

The first synthetic detergents widely used in household and industry were the sodium alkyl sulfates which originated from fats. Today most of the "syndets" used in the household are of non-fat origin, principally derived from petroleum. These are the sodium aryl alkyl sulfonates. Some of the household products containing this detergent are: Vel,® Dreft® (present product changed from sodium lauryl sulfate), Tide,® Surf,® Breeze,® Fab,® Cheer,® Swerl,® and Trend.® There also are liquid type household detergents such as Glim and Joy whose probable composition is indicated in Table I.

The "syndets" are poor cleansers for cotton and hence to make an all purpose cleaner, they are improved by the addition of "builders." The usual "builders" used for this purpose are sodium polyphosphates in concentrations of from 35 per cent to 50 per cent. These "builders" are high-

TABLE I.

Product	Manufacturer	Active Ingredient Approximate Per cent	pH 0.1 Per cent Solution
A. Liquid Dishwashing Compounds:			
Joy	Procter & Gamble	52 per cent solids, chiefly Triethanolamine salt of lauryl sulphate plus a foam stabilizer (also contains about 20 per cent isopropyl alcohol)	6.8
Glim	B. T. Babbitt	55 per cent of a nonionic, ethylene oxide condensation product of an alkyl phenol.	7.4
Lowila Liquid	Westwood Pharmaceuticals	30 per cent alkyl aryl sulfonate	5.0
B. Light Duty, Neutral, Household Detergents:			
Swerl	National Aniline	40 per cent alkyl aryl sulfonate	7.1
Dreft	Procter & Gamble	32 per cent alkyl aryl sulfonate	7.5
Vel	Colgate	33 per cent alkyl aryl sulfonate	6.9

C. Heavy Duty Household Detergents:

For laundering cotton, but used by many housewives for dishwashing also.

Product	Manufacturer	Active Ingredient	Approximate Per-cent Active	Tripoly Phosphate $*Na_5P_3O_{10}$	pH 0.1 Per cent Solution
Breeze	Lever Bros.	Alkyl Aryl Sulfonate	25	42	9.6
Surf	Lever Bros.	Alkyl Aryl Sulfonate	28	40	9.6
Fab	Colgate	Alkyl Aryl Sulfonate	39	36	9.3
Cheer (White)	Procter & Gamble	Alkyl Aryl Sulfonate	22	42	9.5
Cheer (Blue)	Procter & Gamble	Alkyl Aryl Sulfonate	29	46	9.5
Tide	Procter & Gamble	½ Alkyl Aryl Sulfonate ½ Sod. Lauryl Sulphate	22	49	9.5

*Sodium Tripolyphosphate calculated from total P_2O_5 present. Products may contain small amounts of other forms of phosphate.

ly alkaline and transform the essentially neutral syndet into a highly alkaline product for household use with a pH of 9 or 10 in even very dilute solutions (0.1 per cent). Practically all household synthetic detergents, and many soap powders, contain very small amounts of the so-called "optical bleaches." These bleaches are usually derivatives of stilbene disulfonic acid.

These builders and bleaches which are added to the detergent may be just as harmful to the skin as when present in soaps. Of the products listed in Table I, only the liquid detergents and Swerl, Dreft and Vel seem to be free of alkaline builders. Many of the others are "heavily built" and are markedly alkaline.[6]

Soapless Skin Cleansing.—Children as well as adults with atopic dermatitis are often irritated by the use of ordinary soaps. In the past it has been a common practice to clean their skins with inert oils such as mineral oil or olive oil. Demulcents such as starch or oatmeal solutions are helpful and quite soothing in some children. However, none of these agents are good cleansers and may predispose to secondary infections.

A few liquid soapless synthetic detergents are available for skin cleansing. Among these are: Acidolate,® a non-lathering sulfonated oil; Phisoderm,® a creamy emulsion containing the sodium salt of alkyl aryl polyether sulfonate.

Liquid detergents are not as convenient or economical and do not have the same public acceptance for personal hygiene as a detergent in bar or cake form. The difficulty in manufacturing a truly soapless bar has led manufacturers to combine soap with a synthetic detergent. These products do have better action in hard water but since they contain ordinary soap have some of the undesirable qualities of soap. Examples of this type of cleanser are Zest,® a tallow soap combined with sodium lauryl sulfate, and Dermolate,® a combination of soap and sulfated sodium stearate.

For the past five years, we have been interested in the synthetic detergents as cleansing agents in individuals with eczema. Numerous preparations and combinations have been used both in liquid and cake form. Sodium lauryl sulfoacetate in the form of Lowila cake® has received particular attention. This bar is non-irritating, only mildly defatting and of a low sensitizing index. It produces copious suds and has a slippery feel. The lather has a pH of 5 to 5.5 which is approximately that of normal skin.

The antiseptic value of ordinary soap is well recognized. In order to impart antiseptic properties to some of the cleansing agents today, hexachlorophene has been added to such cleansers as Phisohex® and Dial® soap. Sodium lauryl sulfoacetate appears to have bactericidal properties all of its own. It has been used for years in Pepsodent toothpaste and is better known as "Irium."® Read, Fredell and Reddish[10] demonstrated that this detergent did effectively inhibit putrefaction of saliva and did reduce breath odor. In a preliminary group of experiments done by Killian,[5] in which he used the Pohle and Stuart[8] modification of the Price[9] technique, he demonstrated that sodium lauryl sulfoacetate* had the capacity to degerm subject's hands and wrists during usage as a skin cleanser. This antibacterial property is not only immediate but there is a sustained reduction of the bacterial flora of the skin.

In the management of the patient with eczema, a thorough history and complete evaluation of the individual's problem are indispensable. Cutaneous allergic testing should be done. The avoidance of all possible irritants both ingested and contactant is a desirable goal. The success of any treatment in the field of allergy is directly proportional to the ability

*Lowila Cake®—Westwood Pharmaceuticals Division.

to avoid these excitants. The infant and young child's skin is particularly prone to irritation. It has been shown by Klauder and Gross[6] that small babies' skins do not tolerate the alkalinity of ordinary soaps as well as adults. The use of Lowila Cake,® containing sodium lauryl sulfoacetate, as a cleansing agent has been of benefit in the care of the eczematous patient. This material has proven virtually non-irritating. It must be cautioned, however, that too frequent washings with even this hypo-allergic cleanser is not recommended since, like all other detergents, it does produce a mild drying effect. Whenever soap sensitivity is suspected, it is equally important to eliminate the possibility of irritation from the soap deposited in the clothing and bedding used by the child. We prefer a slightly acid liquid detergent specifically designed for this purpose.**

The skins of all newborns and particularly of premature infants are inclined to injury by ordinary soaps. We have observed that the routine use of the soapless lauryl sulfoacetate bar, in all babies, decreases the incidence of soap irritation and aids in the protection against pyogenic dermatoses. We have also observed that "heat rash" or miliaria in children is benefited by avoidance of soap and use of the soapless bar.

Infants with diaper rash or ammoniacal dermatitis are definitely irritated by the alkaline effects of soap. In these babies the use of this non-irritating soapless cleanser, plus the reduction of exposure to the alkaline excreta, leads to immediate improvement.

SUMMARY

1. The composition and properties of ordinary soap are discussed.

2. Ordinary soaps may act as irritants to the skin. This irritation may be due to the alkalinizing effect of soap and "builders," to irritating fatty acids, dyes, preservatives, perfumes, bleaches, germicides, and to medicinal agents added to soap in their manufacture.

3. Soap substitutes such as demulcents, and cleansing oils are unsatisfactory agents in the care of the skin.

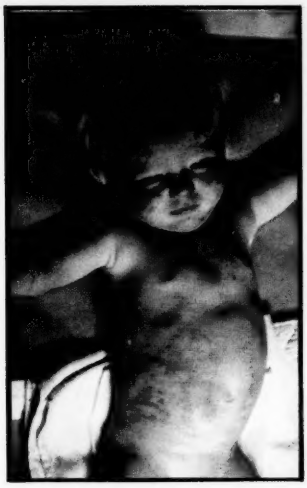
4. The "syndets" are good cleansers, but most household "syndets" are heavily built. The composition of soaps and detergents commonly available are frequently altered by the manufacturers so that one can never be too sure of the causative irritants when a patient complains of dermatitis caused by popular household cleansers.

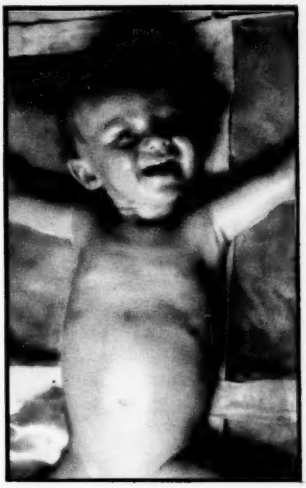
5. Sodium lauryl sulfoacetate, however, has been found to be a most satisfactory cleansing agent when the human skin is irritated by ordinary soap.

6. Since Lowila Cake® is relatively hypo-allergenic, it is most valuable in the treatment of the child with eczema. It also is an ideal cleanser for the skin of the newborn infant, especially the offspring of an allergic

**Lowila Liquid®—Westwood Pharmaceuticals Division.

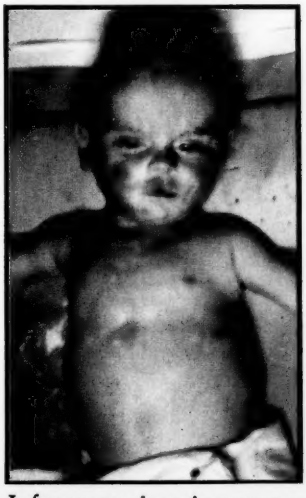
INFANTILE ECZEMA — Results of treatment





The skin should not be cleaned with oil but with a mild soapless cleanser.

Cleansing with the "soapless" cake prevents recurrences initiated by soap.



Infrequent cleansing may cause secondary infection. Too frequent

family. Even the delicate skin of the premature infant is not harmed by sodium lauryl sulfoacetate. A beneficial effect is obtained when Lowila Cake® is employed in the care of "heat rash" or miliaria, and ammoniacal dermatitis.

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616 La Salle Bldg.

PLAYTEX PARK RESEARCH INSTITUTE

Several articles have appeared recently in the ANNALS OF ALLERGY, as well as in *The American Journal of Diseases of Children, American Journal of Obstetrics and Gynecology, Journal of Clinical Investigation,* and other journals publishing articles on research in pediatrics, supported generously by the Playtex Park Research Institute. This institution was founded by the International Latex Corporation and was described as "an experiment in industrial giving." The grants-in-aid of the Institute justify the belief that the sponsor and the governing board had in the concept that industry and medicine can do excellent team work for the common good with great effectiveness.

It is only three and one-half years since the International Latex Corporation established the Institute; it has now become the largest private source of funds for pediatric research in the United States. The tangible results obtained by these grants eventually will help to advance the health of the children of this nation and the world. It is hoped that other industrial organizations will follow suit in this manner, since no other work could be of more value.

DIPHENMETHANIL (PRANTAL) METHYLSULFATE

A New Approach in the Treatment of Poison Ivy Dermatitis

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THIS REPORT deals with the use of diphenmethanil methylsulfate in the therapy of poison ivy dermatitis. The concept that a drug with a cholinergic blocking action might be helpful stems from the reports of Nelson[3,4] who found Prantal effective in relieving pruritus in some cases of neurodermatitis, atopic eczema and vesicular eruptions of the hands (dyshidrotic eczema). According to this investigator, excessive perspiration retarded healing of a concomitant dermatitis in certain instances. The involution of the dermatitis was speeded and the patient relieved with the use of Prantal. According to clinical reports,[1,2,3,4,5,6,7] diphenmethanil methylsulfate, one of the newer synthetic anticholinergic drugs, has a low incidence of undesirable atropine-like side effects. This fact coupled with the reports of Nelson prompted the use of diphenmethanil in this study.

No controls were used in this series of observations on private patients, and these conclusions are based on the comparisons with results obtained heretofore by other methods of treatment. The use of Prantal will probably prevent physicians from using poison ivy extract during the acute stage which is such a dangerous procedure.

METHOD

A series of seventy-three unselected patients with poison ivy dermatitis were treated with oral Prantal.* The drug was given daily in divided doses until complete disappearance of the lesions occurred. Topical therapy was not employed during treatment, although in some instances various lotions or creams had been used by the patient before reporting for treatment. Included in this study are twenty-six children (age five to twelve) who received 50 mg (one-half tablet) three times daily; ten adults, who were given 100 mg three times daily; and thirty-seven adults, who received 100 mg four times daily. Patients were examined every two or three days, and observations of the subject and examiner were recorded at the time of the follow-up visit.

RESULTS

Relief of pruritus was reported by some patients eight to twelve hours after starting medication and by all patients within twenty-four hours. Diminution of "weeping" was frequently reported at twenty-four hours

*Prantal (diphenmethanil methylsulfate—Schering) supplied by George Babcock, Jr., M.D., Division of Clinical Research.

TABLE I. POISON IVY DERMATITIS—TREATMENT WITH PRANTAL

Number Cases	Duration Before Therapy	Daily Dosage of Prantal	Results
26 children (age 5 to 12)	2 to 7 days	50 mg. (½ tab.) t.i.d.	Itching relieved in 12 to 24 hours, oozing stopped in 48 hours. Lesions cleared completely in 3 to 5 days.
10 adults	3 to 5 days	100 mg. t.i.d.	Similar—lesions completely cleared in 5 to 8 days.
37 adults	2 to 7 days	100 mg. q.i.d.	Similar—lesions cleared in 5 days.

and was generally observed to be complete at the time of the first follow-up examination (forty-eight to seventy-two hours). The lesions cleared completely in an average of five days (range—three to eight days). A more rapid result was noted in the group of adults taking 400 mg daily, as compared with those taking 300 mg daily. Side effects of medication were not observed in this series. Results of therapy are summarized in Table I. The following case histories are considered typical.

Case 1.—The patient, a nine-year old boy, was seen forty-eight hours after he developed a rash. On examination large and small vesicles were found to be widely distributed on the back, buttocks, extremities and face. Considerable "weeping" was noted, as well as evidence of scratching. The face and right ear were swollen. A diagnosis of poison ivy dermatitis was made, and the patient was given diphenmethanil 50 mg three times daily without other therapy. Itching was completely relieved in twelve hours. Weeping decreased in twenty-four hours. The face and right ear were normal in appearance in forty-eight hours. Most lesions were dried up at seventy-two hours. On the fifth day all lesions were completely cleared, and the medication was discontinued.

Case 2.—The patient, a twenty-five year old man, was seen five days after the development of a rash on both arms, both wrists, face, and neck. The patient had used several lotions without noticeable benefit. He complained of burning and itching in the areas of the lesions. Examination disclosed extensive weeping vesicular dermatitis of the areas mentioned. Diagnosis—poison ivy dermatitis. Therapy—diphenmethanil 100 mg four times daily. Relief from itching and burning was reported after the second tablet. Lesions almost completely cleared after three days of treatment. Therapy discontinued.

DISCUSSION

The relief of pruritus afforded by Prantal decreases the urge to scratch and thereby helps to promote healing of the lesions and minimize the risk of secondary infection, especially in children. The manner in which Prantal exerts its antipruritic effect is unknown. Perhaps this effect is mediated through the cholinergic blocking action of the drug.

Conceivably a diminution of sweating might also be helpful in poison ivy dermatitis as it was in certain other dermatoses reported by Nelson. Certainly, any irritant effects which sweat might have on the lesion are avoided by the use of an effective anhydrotic agent such as Prantal.

CONCLUSIONS

1. Prantal orally in doses of 100 mg four times daily relieves pruritus, decreases weeping and promotes healing in poison ivy dermatitis.
2. Prantal is well tolerated by children and adults in the dosage employed.

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191 South Avenue

THE AMERICAN ACADEMY OF APPLIED NUTRITION

About 1930 a group of Los Angeles dentists became convinced that there must be a way to reduce the alarming prevalence of dental caries. For research in this subject they formed a study group which soon attracted the attention and attendance of physicians and other scientists interested in nutrition. In 1936, because of the need for a broader base, a new organization was formed, The American Academy of Applied Nutrition.

It was soon felt that malnutrition was the common denominator of many ills and that an educational program, to be effective, should include professions using nutritional knowledge in practice, plus all those concerned with food from earth to table. Therefore laymen were included as associate members.

The objects and purposes of the new organization were set forth in the constitution in part as follows: "The object of the Academy shall be to promote and advance the science and art of nutrition especially as it pertains to the prevention and treatment of disease—to encourage the study of the relationship of nutrition to general medical and dental practice—to provide for the dissemination of knowledge concerning nutrition and related sciences. This corporation is not organized for profit or pecuniary gain."

To better promote the above ideals, the Academy reorganized in 1946 on a national scale and qualified itself to assume responsibility for tax-free gifts.

Dr. Weston A. Price was the first donor who honored the Academy with a life time collection of research material and funds for its advancement. He also gave the Academy his pioneer book, "Nutrition and Physical Degeneration." This important work, which may be obtained from the National Office, describes extensive world-wide studies among native populations. The findings strongly suggest that tooth decay, dental malformations and perhaps other degenerative diseases are primarily nutritional in origin.

In 1951, it was decided that mixed attendance at scientific programs was unsatisfactory from both professional and lay standpoints. Therefore, the American Academy of Applied Nutrition was divided into two components—The American Academy of Nutrition for those with a doctorate and the American Nutrition Society.

(Continued on Page 589)

ADENOTONSILLECTOMY AND ITS RELATION TO ASTHMA

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Rockville Centre, New York

THE PROBLEM of the relationship of tonsils and adenoids to bacterial asthma is as disputed today as it was fifteen years ago. There are three major schools of thought on this subject:

1. Tonsils and adenoids can act as foci of infection. When these foci of infection are removed, the asthma will be favorably influenced.[2,4] When the tonsils and adenoids are infected in a potentially asthmatic patient, early removal can prevent asthma.

2. Tonsils and adenoids play an important role in preventing the spread of infection from the upper respiratory passages to the lower respiratory tract.[6,7] Removal of the tonsils and adenoids may precipitate asthma in an allergic individual. Removal of the tonsils and adenoids may convert a mildly asthmatic patient into a severely asthmatic patient. Physicians should be more conservative in removing tonsils and adenoids in allergic than in non-allergic patients.

3. Indications for adenotonsillectomy are the same for allergic and non-allergic patients. When tonsils and adenoids are diseased or abnormally enlarged, they should be removed in allergic as well as non-allergic patients because of the existing pathology. They should not be removed with the view of primarily affecting the asthmatic condition.[1,3,5,8] Tonsils and adenoids have no bearing on the basic allergic process.

The unsettled problem of bacterial allergy has led to much confusion in the treatment of asthma. The patients are equally confused because of the different opinions. One of the most frequent questions which is asked for patients who present the problem of upper respiratory infection followed by asthma is, "What will removal of the tonsils and adenoids do for my child's asthma?" Because of the three conflicting opinions present today, the family will get one of three answers or all three answers, depending on how many physicians are consulted.

1. Operation will help the asthmatic condition.
2. Operation will make the asthma worse.
3. Operation will not make any difference to the course of the asthma.

CLASSIFICATION OF PATIENTS

The histories of 100 asthmatic patients were reviewed previous to allergic management. Only those patients in whom infection played the dominant role were included in this survey. Of these 100 asthmatic

Presented before the Ninth Annual Congress of the American College of Allergists, Chicago, Illinois, April 28, 1953.

patients, thirty-two did not have adenotonsillectomies, the remaining sixty-eight patients had adenotonsillectomies before coming under allergic management. These latter sixty-eight patients were further subdivided as to the onset of asthma in relation to the tonsillectomy. Forty patients had

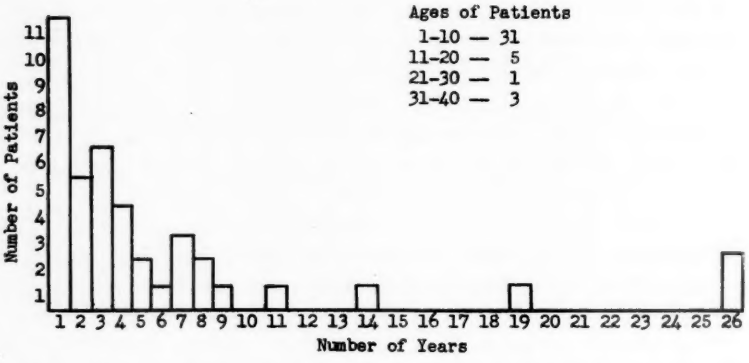

Fig. 1. Onset of asthma after tonsillectomy and adenoidectomy in patients not under allergic management.

the operation performed before the onset of asthma and twenty-eight had the adenotonsillectomy performed after the onset of asthma.

In reviewing these 100 cases with infectious asthma, it was noted that there was more than one adenotonsillectomy performed in seven patients. In some of these seven patients, because of constant regrowth of the adenoids, the adenoidectomy was repeated as often as four times.

Only four patients out of 100 patients studied in this survey had adenotonsillectomies after coming under allergic management.

The age distribution in this study was eighty-one patients in the one to ten age group; ten patients in the eleven to twenty age group; two patients in the twenty-one to thirty age group; and seven patients in the thirty-one to forty age group.

The major causative factors in the 100 asthmatic patients studied were infection, or infection and inhalants (pollen, dust, et cetera). Since the problem was primarily infection, all asthmatic patients who did not show aggravation of symptoms due to infection were eliminated.

RESULTS

Of 100 patients with bacterial asthma, sixty-eight had adenotonsillectomies before coming under allergic treatment. These sixty-eight patients were further subdivided as to the onset of asthma in relation to this operation. There were forty patients who developed asthma for the first time after adenotonsillectomy. The length of time for asthma to occur after adenotonsillectomy is shown on Figure 1. Twenty-eight per cent of the

patients, the greatest percentage, had their first occurrence of asthma within the first year after adenotonsillectomy. A total of forty per cent of the patients had their onset of asthma within two years, and a total of fifty-four per cent had their first attack of asthma within the three years after removal of tonsils and adenoids.

There were twenty-eight patients before coming under allergic management who had adenotonsillectomies after the onset of their asthma. Figure 2 shows the length of time for asthma to recur after removal of the tonsils and adenoids. Eighty-two per cent of the patients had recurrence of the asthma within the first year after adenotonsillectomy. There was a total of 89 per cent recurrence within two years and 100 per cent recurrence of asthma within four years after adenotonsillectomy.

The patients in the two groups (asthmatics without and those with tonsils and adenoids) were graded as to the severity of their asthma. The asthma was classified as mild, moderate, or severe. Figure 3 illustrates that there are essentially the same percentages of mild, moderate, and severe asthma in the group that had retained their tonsils and adenoids, and the group in which they had been removed.

DISCUSSION

Figure 1 shows the interval of time after adenotonsillectomy for initiation of asthma in patients before coming under allergic treatment. Twenty-eight per cent, the greatest percentage, had their first onset of asthma within the first year after adenotonsillectomy. This high incidence of asthma in the first year after removal of tonsils and adenoids suggests that adenotonsillectomy predisposes to the early onset of bronchial asthma in allergic patients. However, on analyzing the reasons for adenotonsillectomy in the entire group that developed asthma for the first time after this operation, the usual indications were noted, i.e., repeated sore throats, ear infections, enlarged adenoids, and recurrent colds. The most frequent reason was "recurrent colds." On analyzing the indications for adenotonsillectomy in the group that had their onset of asthma within the first year following this operation, it was noted that over 80 per cent were done because of "frequent colds." It is highly suspicious that a large number of these patients may have had an allergic vasomotor rhinitis and not an infectious process. No nasal smears were taken before the adenotonsillectomy. The operation was advised because of repeated infection but there was no laboratory evidence (i.e., nasal smear) to confirm the diagnosis of infection. It is unknown how many allergic patients had asthma precipitated as a result of adenotonsillectomy, and how many would have developed asthma as an inevitable step in the progression of the allergic process.

Unfortunately the exact months of the year that adenotonsillectomy was done before coming under allergic treatment was not recorded in all of

my figures. However, it was noted that four cases were performed in the ragweed pollen season with immediate onset of severe bronchial asthma. It is our policy to perform adenotonsillectomies during periods of pollen freedom in the east on all allergic patients.

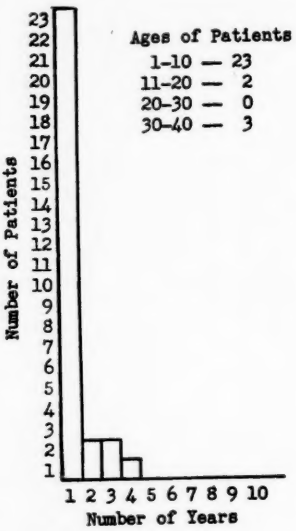

Fig. 2. Recurrence of asthma after tonsillectomy and adenoidectomy in asthmatic patients not under allergic management.

On analysis of Figure 2, it is seen that 82 per cent of the asthmatic patients (before coming under allergic management) had recurrence of their asthma within the first year after adenotonsillectomy. On investigation of the reasons for removal of the tonsils and adenoids, it was found that over 90 per cent were done because of "chronic running nose," "recurrent colds," or to relieve the bronchial asthma.

The results of these statistics show that the indication for adenotonsillectomy must be more carefully evaluated. It is important to clearly differentiate an allergic vasomotor rhinitis from a true recurrent cold. It is also important to differentiate an allergic vasomotor rhinitis with secondary infection, from infection without underlying allergy. History and physical signs are often misleading guides in establishing the diagnosis. A very important tool which should be used more often is the nasal smear for eosinophils. Repeated nasal smears will differentiate allergy from infection. The otorhinolaryngologist performs bleeding and clotting times on all patients before removal of tonsils and adenoids. It should be routine to

do repeated nasal smears on all suspicious cases where the diagnosis is in doubt. When the nasal smear shows repeated counts for eosinophils of greater than 10 per cent, allergic treatment should be instituted first. If indications for adenotonsillectomy still exist after allergic management,

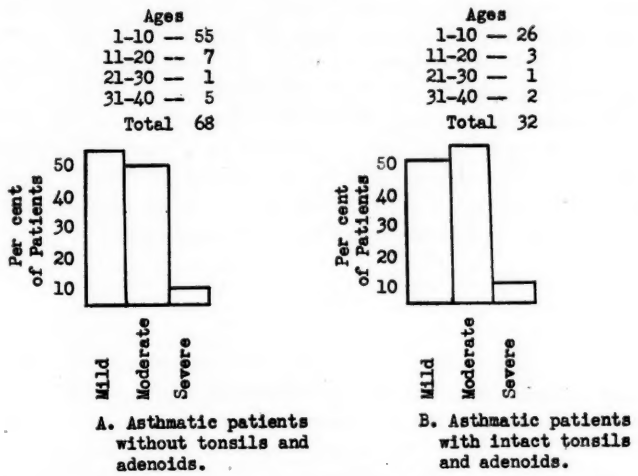

Fig. 3. Severity of asthma in patients with and without adenotonsillectomy.

it should be performed during a pollen free period. When adenotonsillectomy is done primarily to relieve the allergic condition, it will often end in failure.

Seven per cent of the patients had more than one adenotonsillectomy before coming under allergic management. A similar number is noted by other authors.[3] The allergic condition is often unrecognized and surgery is performed with the view of correcting the persistent nasal trouble. This ends in failure. Whenever there is regrowth of adenoid tissue, it is wise to suspect allergy before repeating the adenoidectomy.

Only 4 per cent of the patients were sent for adenotonsillectomy after allergic treatment was instituted. This low number indicates that many of the indications for this operation no longer exist after proper allergic treatment is instituted. There was no flare up of asthma following adenotonsillectomy in patients who had been under allergic treatment.

There are two diametrically opposed schools of thought today on the function of the tonsils and adenoids. One group believes these lymphoid tissue act as the first line of defense in preventing the spread of infection from the upper respiratory tract to the lower respiratory tract. The second group believes that if the tonsils and adenoids are a focus of infection or potential source of infection, they should be removed as early as

possible to cure or prevent asthma. Theoretically, if the tonsils and adenoids play a protective role, there should be less severe cases in the group with the lymphoid tissue intact; conversely, if the tonsils and adenoids play an important role as foci of infection or potential foci of infection, there should be less severe cases in the group that had adenotonsillectomies. Figure 3 shows that there is approximately the same percentage of mild, moderate, and severe asthmatics in both groups. Since the two groups are essentially the same, the severity of asthma does not bear any relationship to the presence or absence of tonsils and adenoids.

The indications for adenotonsillectomy that we follow are the same for allergic and non-allergic patients. Operation is advised if the tonsils or adenoids are excessively enlarged thereby causing obstructive symptoms, repeated ear infections, loss of hearing due to enlargement of adenoids, repeated tonsillar infections, or chronic cervical adenitis.

SUMMARY

1. A total of 100 patients with infectious asthma were studied in this survey. Thirty-two patients did not have adenotonsillectomies and sixty-eight had had adenotonsillectomies before coming under allergic treatment.

2. In the group of sixty-eight patients who had their tonsils and adenoids removed before coming under allergic treatment, forty patients developed asthma for the first time after adenotonsillectomy and twenty-eight patients had asthma before adenotonsillectomy.

3. In the forty patients who developed asthma for the first time after adenotonsillectomy, 28 per cent developed asthma within the first year after the operation. A total of 40 per cent developed asthma within two years after adenotonsillectomy. The indications for removal of tonsils and adenoids were predominately for "chronic running nose."

4. In the twenty-eight patients who had asthma for varying lengths of time before adenotonsillectomy and prior to coming under allergic management, 82 per cent had recurrence of asthma within the first year after removal of the tonsils and adenoids. The reasons for operation were chronic rhinorrhea and to relieve the asthma.

5. There is approximately the same percentage of mild, moderate, and severe asthma in the group with intact tonsils and adenoids, and in the group that have them removed.

CONCLUSIONS

Too many adenotonsillectomies are performed because allergic vasomotor rhinitis is confused with recurrent colds. Nasal smears should be performed to help differentiate the two conditions. When the nasal smear is positive for eosinophils, allergic treatment should be instituted first. Very often indications for adenotonsillectomy disappear after allergic treatment is instituted. If indications for adenotonsillectomy still persist after

allergic treatment, it should be performed during a pollen free period. When adenotonsillectomy is performed primarily to relieve the allergic condition, the results are unsatisfactory. The indications for adenotonsillectomy are the same in allergic and nonallergic individuals. The presence or absence of tonsils and adenoids made no difference in the severity of asthma.

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165 North Village Avenue

THE AMERICAN ACADEMY OF APPLIED NUTRITION

(Continued from Page 582)

Henceforth, while the Academy will determine policies for both groups, convention programs will be separate.

Publications include the *Journal of the Academy of Nutrition,* designed as a quarterly but sometimes published less often, and *Modern Nutrition,* a monthly magazine sent to members of both Societies.

At the recent annual meeting held in Pasadena, California, in May, papers included such titles as: "Vitamin C Therapy of Infectious Diseases;" "Etiology of Dental Caries;" "Allergy and Nutrition;" "Coronary Thrombosis—An Etiological Study;" "Relationship of Nutritional State to Poliomyelitis" and others of much interest. Most of the papers will be published and become available to members.

Study groups and chapters exist in various cities and are encouraged as a means of increasing nutritional knowledge. It is hoped that in the near future the Annual Convention may be held in the mid-west rather than in California.

Officers for 1953-54 are as follows:

President: James W. Carson, D.D.S., F.A.C.D., Los Angeles, Calif.
President-elect: Granville F. Knight, M.D., F.A.C.A., Santa Barbara, Calif.
First Vice President: N. Philip Norman, M.D., New York, New York.
Second Vice President: Frank E. Koepel, D.D.S., Detroit, Mich.
Secretary: W. D. Currier, M.D., Pasadena, Calif.
Treasurer: Harold Stone, D.D.S., La Habra, Calif.

The Academy of Nutrition will welcome qualified new members interested in the application of nutritional knowledge to the healing arts. The subject is one of vital and rapidly increasing importance. Further information may be obtained from Mrs. Beth Bunch Medearis, Executive Secretary, American Academy of Nutrition, 6238 Wilshire Boulevard, Los Angeles 48, California.

SENSITIVITY TO GRAPE AND GRAPE PRODUCTS, INCLUDING WINE

Case Report

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

THE FOLLOWING case history is presented at length, and in detail, because it exemplifies so many different facets of the practice of allergy.

The patient, a Catholic priest aged thirty-one, had been referred by his personal physician with a diagnosis of hay fever, bronchial asthma, and urticaria.

Present complaint: Sneezing, nasal stenosis, with a watery coryza, perennial, with seasonal exacerbations in March and April, for six years. Attacks occur at any time during the day, both in the patient's own quarters and in church, with no relation to food or environment, or any special set of circumstances, excepting that minor transient episodes inconsistently occurred with marked change in temperature and while handling cold or damp objects.

A cough, productive of white, frothy, and occasionally thick lumpy mucus, has been present intermittently and altogether for eight years, and more consistently during the last four, markedly with colds, and especially during winter and early spring. The cough occurred perennially, with "choking and gagging," spells lasting one to two minutes, once or twice daily, noticeably at bedtime. It was worse with massive exposure to tobacco smoke, and frequently associated with exposure to marked temperature change. Fatigue, emotion and nervous tension sometimes increased coughing, which rarely awakened the patient once or twice nightly. It was relieved by neither proprietary nor prescribed ant'tussive medications.

The wheezing, of three years' duration, was rarely inconvenient, and was obvious chiefly at night and when the patient was otherwise affected by upper respiratory infections. It was worse indoors, and had been present in all environments and in all rooms of the house, being no worse in the patient's own cell, where he spent the greater part of his time. The wheeze was worse with hearty laughter, and when heavy physical work was being done.

The uriticaria began seven months before the patient's first visit. It not only affected the skin, with typical wheals and generalized pruritus, but also the mucous membranes of the mouth, and especially of the throat, causing swelling of the glottis and a peculiar, rasping cough, associated with gasping for breath, different from the cough described above occurring occasionally, but with no hives. When urticaria were present, the second type of cough came on occasionally in paroxysms lasting up to ten minutes. It was especially noted after meals, and with the ingestion of sweets. It was sometimes present when all other symptoms were absent. There were no other complaints, excepting rare temporal headaches, worse with nasal stenosis.

Past history: tonsillectomy and adenoidectomy at age of eight; bronchitis in January, 1952; boils lanced (two) October, 1952; chest x-rays at yearly intervals; no abnormalities were discovered. The patient's numerous physical examinations, usually at yearly intervals, showed no departure from normal health.

Family history: mother, sick headaches, but otherwise non-contributory.

Physical examination: the patient was a well-developed, well-nourished man, essentially in normal health, excepting for evidence of moderate nasal stenosis and moderate emphysema. The skin was blotchy, but no urticaria were present. All systems were within normal limits. Blood pressure was 130/80; weight, 209 pounds;

height, 5 feet ten inches; pulse, 88, with regular rhythm; vital capacity, 5200 cc, 90 per cent of the air being expired within three seconds.

The laboratory studies showed the urine to be acid in reaction, specific gravity 1.021, negative for albumin and glucose. The blood presented a hemoglobin of 105 per cent (16.4 gms) for a red cell count of 5,110,000. The color index was 1.03. The white blood cells numbered 9,100, for a differential count of 59 per cent polymorphonuclear leukocytes, 1 per cent band forms, 35 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophils. The blood smear was that of normal health. The blood sedimentation rate was 2.0 mm for twenty minutes, and 12.0 mm for one hour. The Hinton test was negative. Blood was taken on January 13, 1953, and June 11, 1953, for passive transfer.

X-ray of the chest and sinuses in March, 1953, showed both apices to be of normal radiance. The hilus shadows were moderately increased in width and density. There was peribronchial thickening of the middle and lower lung fields, and moderate emphysema of the lower lung fields. The diaphragms were low. The posterior mediastinum and costophrenic angles were clear. The trachea was in the midline. The shadow of the heart and great vessels was within normal limits. There was widening of the lower interspaces bilaterally. There was no abnormality in the ribs.

The x-ray of the sinuses showed a slightly diminished radiance over all the nasal accessory sinuses, this change being somewhat more marked over the posterior ethmoidal cells and the antara, consistent with thickening and hypertrophy of the mucous membranes. Studies with the patient in the erect position revealed no evidence of a fluid level.

Psychiatric Interview: The patient was a well balanced, adjusted, happy individual, with a true vocation for his work, cheerfully accepting the restrictions of monastic life with no resentments. He was popular with his pastor and two assistant priests and extremely popular with the people of the parish. The Minnesota Multiphasic Personality Profile was within normal limits.

Environmental Survey: The patient occupied, with two other priests, a dry, well-situated one-family house, one quarter mile from a textile factory, and a half mile from a railroad. The attic and basement were occasionally damp in prolonged wet weather. Both were kept completely closed, the patient having no access to either. Each occupant had his own room and all three convened only for meals and religious exercises in church. The house was heated by oil. There were woolen rugs, vacuum cleaned for one or two hours, three times weekly. Flowers were present only on high holidays. There were five beds, with fillings of down, feathers and cotton. There were cotton bedspreads. There was one cocker spaniel, kept outdoors, and one canary, indoors.

Food Check List: The diet was nourishing and well-balanced for all factors, excepting for excessive salt ingestion. The patient noted that he suspected haddock, apple, cranberry, grape, peach, pear, tangerines and watermelon as occasionally causing indigestion, and sometimes exacerbation of symptoms. The patient had never ingested alcohol socially. He did not smoke.

Skin Tests: Using the weakest and strongest solutions, by the intradermal method, there were no positive skin tests to the common inhalants, cereals, meats, nuts, spices, fish, fruits, vegetables, molds and pollens. There was a 2 plus to 3 plus test to timothy, in the 2,000 p.n.u. strength, corroborated by successive testings. During the testing period, but with no medication taken for twenty-four to forty-eight hours before each office visit, the patient took Chlor-Trimeton, Benadryl, Lergigan, Co-Pyronil, Pyribenzamine (plain and delayed action) and three additional numbered, but as yet not named antihistaminic agents—AH2526, 4445, and 1532, with no effect upon any of his symptoms, although some were taken in double the usual therapeutically recommended doses. Side reactions of drowsiness

and bad taste were noted. Mercodol syrup in 10 to 20 cc doses had no effect on either of the coughs. Cortone by mouth, in initial doses of 300 mg daily, was without effect. Pyromen was given as part of an evaluation study, with no noted decrease in any of the symptoms. The antihistaminic agents were reported as decreasing itching "50 per cent."

Treatment: dust precautions were initiated in the patient's own room, with no appreciable change in his symptoms. He was then placed on a very restricted diet, which included only tea, rice, lamb, apricots, cherries, peaches, cranberries, prunes, gelatin, cane sugar, beets, beet greens, spinach and sweet potatoes, for a period of three weeks. It was understood that during this time he could continue saying Mass, and therefore it was known that he would be taking small quantities of wheat and grape wine. The diet was known to include cranberry, which the patient suspected. There was neither exacerbation nor amelioration of symptoms, excepting for a change in the pattern of reaction, the cough, pruritus and urticaria, as well as the nasal stenosis, all occurring simultaneously, being worse each morning about ten minutes after Mass. Grape wine fell under suspicion. The patient was therefore (for the first time) tested to grape and raisin, given large positive reactions not only to intradermal test, but by pressure puncture, to grape juice (Welch's). The second blood sample was then taken for passive transfer studies.

Two weeks later the patient was given two ounces of wine to drink. Within ten minutes he had a violent constitutional reaction, with injected conjunctivae and epiphora, sneezing and coryza, cough, wheeze, and generalized angioneurotic edema and urticaria. This was treated with epinephrine 1:1000, 0.3 cc subcutaneously, repeated in twelve minutes. Susphrine (Brewer) 0.3 cc was given subcutaneonsly in thirty minutes. The signs and symptoms diminished slowly over a period of four hours, persisting in some degree for forty-eight hours.

Two weeks subsequently, grain alcohol, 20 cc diluted with water to the same concentration as the wine (12 per cent) was ingested, with no untoward effect. Beer, 8 oz, and whiskey ingestion caused no symptoms.

It was arranged for the patient to say no Mass for two weeks. Within fifty-six hours all symptoms cleared, although funeral Masses (at which wine is not ingested) were said. On one occasion the ingestion of wine caused symptoms, arising in fifteen minutes and lasting three days. Arrangements were made for the wine to be limited to 5 drops, to which was added one drop of water, once daily. The symptoms were milder, but otherwise continuously present.

Repeat tests with grape seed extract (furnished by Hollister-Stier) gave a 3 plus reaction to the 1:1000 dilution.

Oral desensitization was attempted during the patient's vacation period. Welch's grape juice was diluted to 1:10,000, 1:1000, 1:100 and 1:10. Successive doses once daily consisted of 1, 2, 4, 8, 12, 20, 30 and 50 drops in one ounce of water. In the absence of symptoms, the patient was to take successive doses of 5, 10, 15, 20, 30 and 50 drops of the next succeeding concentration. No symptoms occurred until the dose of 50 drops of the 1:100 dilution was ingested, resulting in irritation of the throat, vigorous coughing, progressing to wheezing. Five drops of the 1:10 dilution, several days later, caused similar symptoms.

The patient had volunteered the belief that citrus fruit ingestion played a contributory role. Although tests were absent in the routine strengths used, their elimination caused lessening of the difficulties, estimated by the patient as 30 per cent.

Passive transfer (recipient, E.A.B.) to grape, grape seed, commercial grape juice, lemon, lime, orange and grapefruit, showed the following reactions: all were moderately positive in the test sites; completely negative in the recipient's skin. Buffered saline control tests in the passive transfer site and the skin were both negative. The subsequent ingestion of grape juice did not reactivate the sites, excepting for slight local pruritus.

It is concluded that the patient had marked sensitivities clinically and by skin test to grape juice, grape seed, and Welch's Grape Juice, and that he was clinically sensitive as well to citrus fruits, with positive passive transfer but negative direct skin tests.

The patient's vocation makes it impossible for him to take his part in a religious community unless he says Mass. The ingestion of grape (in any form) causes coryza, cough, bronchospasm, and urticaria, ameliorated to a moderate degree by prophylactic and therapeutic medication. In the same environment, under exactly similar circumstances, as in attending (but not saying) Mass, no symptoms occur.

AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics held its twenty-second annual meeting at the Biscayne Terrace Hotel, Miami, Florida, October 3, 1953. Dr. Robert H. Trimby acted as chairman of the morning session of the Allergy Section, with Drs. Norman A. Pokorny, Joseph Weiner, Norman W. Clein, Roland B. Scott, and Maurice Kaufmann participating. Dr. Edward P. Duffy, Jr., was chairman of the afternoon session, with Drs. Bret Ratner, Jerome Glaser, A. Matheson, Arthur J. Horesh, and James C. Overall participating. There was a panel discussion in the evening with Dr. Bret Ratner as moderator, and members of the panel were Drs. Susan C. Dees, Gerald M. Cline, Morton Zall, James C. Overall, Jerome Glaser, Arthur J. Horesh, and Norman W. Clein.

ASSOCIATION OF MILITARY SURGEONS

The sixtieth annual meeting of the Association of Military Surgeons will be held at the Statler Hotel in Washington, D. C., November 9, 10, 11, 1953.

NOTICE

On page 364 of May-June ANNALS, in the Proceedings of the Ninth Annual Congress, Members of the Nominating Committee from the College-at-large should read: Drs. John H. Mitchell and Harry L. Rogers.

EFFECT OF EPINEPHRINE OINTMENT ON THE SCRATCHED HUMAN SKIN

EDWARD A. AMES
Cold Spring Harbor, New York

IT HAS recently been shown[1] that it is possible to stabilize epinephrine for long periods against oxidation when the epinephrine is suspended under special conditions in petrolatum. The stabilized epinephrine ointment has been shown to be active in relieving symptomatically certain itching dermatoses of the skin. However, the mechanism of action is not quite clear. It was pointed out that, in general, when the skin is broken, the vasoconstrictor and anti-pruritic action of epinephrine is observed. However, there are also certain skin conditions in which lesions are present but no blanching or vasoconstriction is observable. For example, in applying epinephrine ointment of this type to the dermatitis produced by poison ivy, only certain areas of the skin, ostensibly uniform in terms of the lesions present, blanched. It was deemed desirable, therefore, to study in some detail the action of this stabilized material on a standard scratch in the human skin. The standardization of scratches in the human skin is made possible by the scratcher devised by Morrison.[2] This has been described in detail and need not be discussed here except to say that it has proved satisfactory in our hands. Out of quantitative data of the type to be described in this connection, some element of predictability with respect to the optimum concentration to be used in the therapy of the dermatoses may be expected. These expectations are to a certain extent borne out by the data to be presented.

The systematic quantitative study of the vasoconstrictor action of epinephrine base ointment on the human skin is readily studied by observing the blanching area caused by different concentrations of the ointment rubbed into scratches of a usefully constant and consistently equal depth. In a typical experiment, three observations were usually made: (1) the time from the contact of the ointment with the scratch to the first appearance of blanching, (2) the area of the blanching (at several different times) and (3) the duration of the blanching (*area* at a *point*). By comparing these three aspects for each different concentration of the base ointment, it was hoped that a useful measurement of the blanching effect of epinephrine ointment could be assayed.

The ointment used was stabilized to prevent oxidation of the epinephrine base by the addition of propyl gallate. The primary dilution was 1:500 in petrolatum. It was then diluted by weight with mineral oil to a 1:1000 suspension. Concentrations down to 1:5,000,000 were made serially by

From the Biological Laboratory, Cold Spring Harbor, Long Island, New York. This research was supported by a grant from the Josiah Macy, Jr., Foundation, New York City.

volume, using mineral oil. A Morrison scratcher was used to make the scratches. Although it was shown that a very slight change in the depth of the scratch would produce a marked change in both the area and time of blanching, it proved possible to achieve reasonably consistent results using

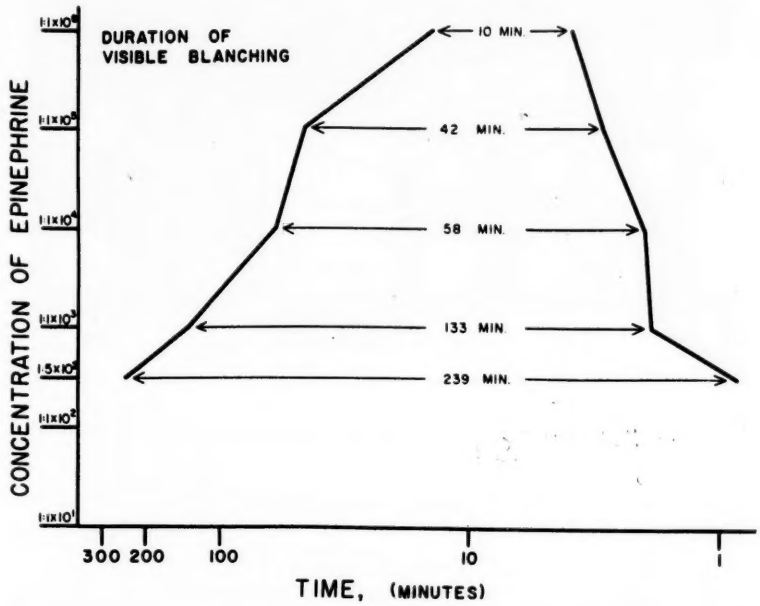

Fig. 1. This illustrates that when the starting time for blanching increases with diminishing concentrations of epinephrine, the duration of the blanching time decreases. The duration of visible blanching, for example, is 239 minutes with 1:500 epinephrine, 133 minutes with 1:1,000 epinephrine, and 58 minutes with 1:10,000 epinephrine.

this technique. The area blanched was traced in ink on cellulose acetate; ultra-violet light was used since it is a constant source of illumination and more clearly defines the blanched area.

It was found that three variables in the data taken for every scratch had a fairly definite relationship to each other, and this relationship was the same regardless of scratch depth or the concentration of the epinephrine. These parameters were: the time of the first blanching, the skin area blanched, and the duration of the blanching. The time for the blanching to first appear decreases as an increase occurs in (1) the area of the blanching, and (2) the duration of the blanching. This is shown in Figures 1 and 2. Figure 1, an average of experiments illustrates that when the starting time for blanching to appear increases, the duration of the blanching time decreases. Figure 2 shows that as the starting time for blanching increases from "A" toward "B," with decreasing concentrations

the blanched area decreases from "F" toward "E." The above occurred in all experiments. However, the correlation between the concentration of the epinephrine and the time before blanching appears and therefore the other two factors mentioned above can only be stated definitely if the

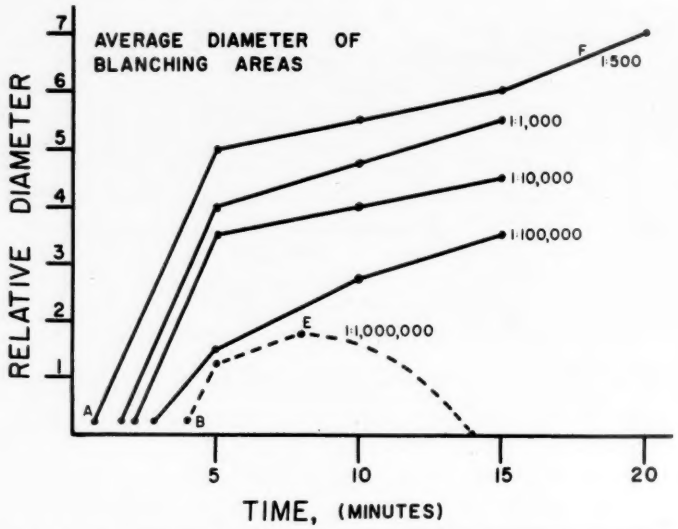

Fig. 2. After starting time for blanching increases from A to B with decreasing concentration, the blanching area also decreases from F to E. These data are the average diameter of the blanched areas as observed under ultraviolet light.

depth of the scratch remains constant. It can be shown (Fig. 3) that a lower concentration of the base ointment can cause a larger blanched area than a higher concentration if the scratch for the former is deeper than the scratch for the latter. It can also be shown (Fig. 3 and 4) that if the concentration of the base ointment is constant, the starting time, area, and duration of the blanching effect, can be controlled completely by the depth and nature of the scratch.

The relationship between these variables can be expressed as follows: where the scratch depth is constant, the area of the blanching, the duration of the blanching, and the time it takes for blanching to occur is short, the blanching lasts a long time, and has a large area.

In most tests, scratches were of a depth to cause very slight subcutaneous bleeding. If pronounced bleeding occurred, it was stopped at first by the action of the epinephrine but then began to bleed as the effect of the ointment wore off. If the bleeding occurred before application of the epinephrine in a deep enough scratch to produce external bleeding, the immediate area could not be made to blanch by tested concentrations up to

and including 1:500 epinephrine ointment. In a typical case where 1:500 ointment was used, bleeding overcame the blanching effect of the ointment for about twenty minutes. This factor of bleeding may be a limiting factor in the depth of a scratch necessary to produce the maximum blanching

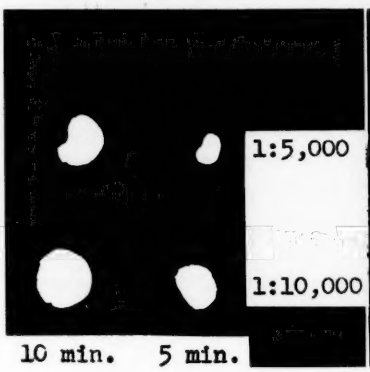

Fig. 3.

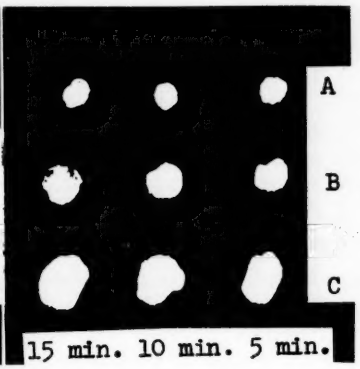

Fig. 4.

Fig. 3. Influence of scratch depth on area. This diagram and Figure 4 show the blanching area as traced on cellulose acetate. Two scratches were made and 1:5,000 ointment rubbed into the shallow one and 1:10,000 rubbed into the slightly deeper one. Although containing a lower concentration of epinephrine base, the blanching resulting from the use of 1:10,000 ointment grew to a larger size and obtained this size more quickly than the more concentrated 1:5,000 ointment due to the deeper scratch used for the former.

Fig. 4. Influence of scratch depth on time. The results of 1:500 epinephrine ointment rubbed into three scratches. "A" being the shallowest and "C" the deepest. The size difference is evident, the deeper scratch producing the larger blanched area. The starting time for the blanching decreases from "A" to "C" (1 minute, 30 seconds; 1 minute, 20 seconds, 1 minute), and the duration of the blanching increases from "A" to "C" (From 35 minutes, to 1 hour, to 2 hours and 30 minutes).

area. The scratches and blanching areas represented in the graphs are reasonably close to the maximum areas that could be blanched using any one concentration of epinephrine. In general, the blanching area takes the form of a circle around the scratch; although, as previously mentioned, bleeding accounted for most irregularities in shape.

The ointment never caused any apparent irritation except for a general reddening of the skin around the blanched areas.

DISCUSSION

The data illustrate, especially in Figure 2, that when epinephrine ointment is applied to dermatoses blanching may be expected if any effect is to be obtained within a period of five minutes irrespective of the length of time and the area that the blanching will persist. Comparison of 1:500 and 1:1000 epinephrine discloses that there is little to be gained by using

1:500 epinephrine and that this is almost as effective within the limits of error of our experiment as 1:1000 epinephrine. However, as the dilution of epinephrine further increases the anticipated therapeutic result decreases. It appears from the data previously reported that with dissolved epinephrine salts, 1:5000 epinephrine undecylenate, for example, is about as effective as 1:5000 base. However, there are many advantages to be obtained by using the base because of the greater stability achieved. Further, it is evident from our data that at least 1:10,000 epinephrine base should be employed if suitable therapeutic results are to be obtained. Although no constitutional effects have been reported by using epinephrine ointments of this type, 1:1000 epinephrine ointment would appear to be a suitable therapeutic concentration based on the data obtained here.

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SECTION ON ALLERGY

The next regular meeting of the Section on Allergy, Medical Society of the County of Kings and Academy of Medicine of Brooklyn will be held at the Society building on Thursday, November 19, 1953, at 9:00 p.m. On the program will be Dr. Lewis Webb Hill, Associate Professor of Pediatrics, Harvard Medical School, Chief of the Allergy Section, Children's Medical Center, Boston, who will speak on "Respiratory Allergy in Infancy and Childhood." Dr. Bret Ratner, Professor of Clinical Pediatrics (Allergy), Associate Professor of Immunology, New York Medical College, and Attending Pediatrician, Flower and Fifth Avenue Hospital, New York City, will discuss the paper.

CORRECTION

On page 468 of July-August ANNALS, paragraph 4, line 4, should read "be given *intramuscularly,*" and line 6 should read, "be given *intravenously.*"

On page 474, "diagnostic aid is the finding of eosinophiles in the thick ropy saliva."

SPIROGRAPHIC STUDIES OF ASTHMATICS

The Delayed Expiratory Sign

A. E. BACHMANN, M.D.; G. RUIZ MORENO, M.D., F.A.C.A.;
M. A. SOLARI, M.D., F.A.C.A., and MRS. M. C. A. DE LOTHRINGER
Research Institute of the National Academy of Medicine
Buenos Aires, Argentina

SINCE SPIROGRAMS entered everyday practice with the fundamental papers of Knipping[22] and Anthony,[1] many studies have been carried out in asthmatic patients with the object of finding in them some pathognomonic sign or signs. Many authors[4,6,7,9,11,14,17,20,21,26] have come to study the prolonged expiration time in asthma and in emphysema patients, and have found it present in almost every case. As this sign appears to be almost constant in asthmatic patients although not suffering from an asthmatic attack,[5] we undertook the following study with the object of discovering whether it is also present in any other type of wheezing. As it also appears in emphysematous asthmatics, we set out to determine whether the aforesaid constant appearance in the tracings has a prognostic significance in the severity of the asthma affecting a given patient.

MATERIAL AND METHODS

Sixty subjects were studied of ages ranging between twelve and sixty-six. Ten of them who had never (at least apparently) suffered from repeated bronchial disorders or thoracic deformities, were used as controls. Another ten had various chronic affections of the respiratory tract, such as bronchiectasia, fibrosis, emphysema, but no asthma. These were also used as controls. The remaining forty, all asthmatic, were studied clinically with skin and clinical allergen tests, x-rays and laboratory tests, so as to bring them within the outlines of Ruiz Moreno's classification of asthma.[25] After this they were placed in the following three groups: (1) fifteen purely asthmatic (alpha), (2) fourteen unclassified, asthmatic with bronchial infection (gamma), and (3) twelve purely allergic asthmatics with a coexisting bronchial infection (alpha-gamma). The sputum of these last three groups and the group of individuals with non-asthmatic chronic infections of the respiratory tract (omega) were subjected to a careful study using toluidin blue according to Bachmann, Pedace and Ruiz Moreno's technique.[2] Besides, and in order to assess the severity of the asthma in each case, we used the method recommended by Beale, Fowler and Comroe[5] who take into consideration the length and frequency of the illness, and duration and intensity of the attacks.

Finally the controls as well as the asthmatics who were not suffering from an attack were studied with an ordinary Benedict-Roth apparatus, following on general lines Cournand and Richards' procedure.[10] However, in order to determine the delayed expiration in the vital capacity, so as to

avoid any errors in the results, a forced expiration was made first and then the inspiration according to Vaccareza, Lanari, Soubrié and Alberdi's recommendations.[26] After the first spirographic tracing was made, the patients were submitted to nebulizations with a Zárate type of nebulizer[27] with an

TABLE I

Type	Patients	Ronchus Sibilus	Dyspnea	Delayed Expiratory
..	15	11	8	8
..	14	12	9	12
....	12	12	8	12
..	10	5	7	7
..	10			3
	61	40	32	42

.. —Pure allergic asthma.
.. —Unclassified asthma with broncho-infection.
....—Pure allergic asthma with co-existing bronchial infection.
.. —Non-asthmatic respiratory infection.
.. —Normal.

adrenaline substitute (Isorrenin), in accordance with Dautrebande's procedure[12] (ten deep and slow inspirations, with a brief pause after each expiration, then administering ten drops of the preparation). Ten minutes after the nebulization a new tracing was made. To determine the delayed expiration the space between the upward and downward grade of the tracing transformed into seconds was measured at the air level of the reserve in the vital capacity, the basis being the lowest limit of the air current. This measurement was made in three successive reckonings of the vital capacity, registering the average number in the results both for the delay as well as for the vital capacity.

Before and after the tracings, the patients were examined clinically to register the presence or absence of rhonchus and sibilus or any other abnormalities. Also the pulse and blood-pressure were checked.

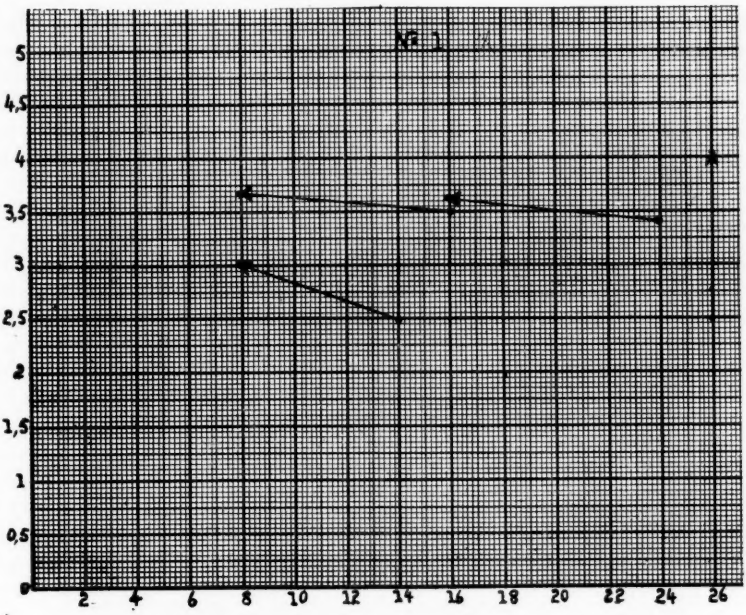
Finally, new spirographic tracings were made in several patients some time after the first, in order to find out if the disorders in these were irreversible.

RESULTS

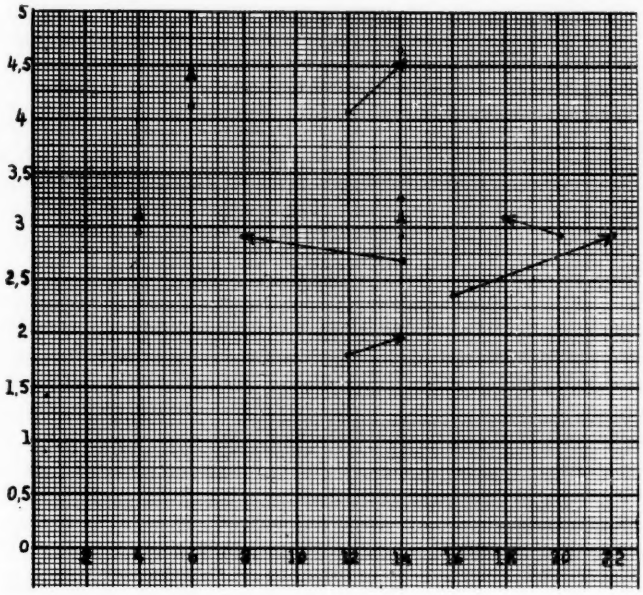
In the chart (Table I) we show the type of asthma or chronic respiratory disorder in each individual, together with the presence of rhonchus, sibilus and subjective or effort dyspnea in the patients at the time the spirographic tracing was made, and the number of times when the delayed expiratory sign was positive (D.E.S.).

It will be seen that delay appeared in all the types under consideration but more frequently in those cases of allergic asthma with unclassified associated bronchoinfection. Moreover, the delay—especially in these last cases—is fairly often associated with the clinical and subjective symptomatology of each patient.

As it is difficult to demonstrate in graphs the severity of the asthma on

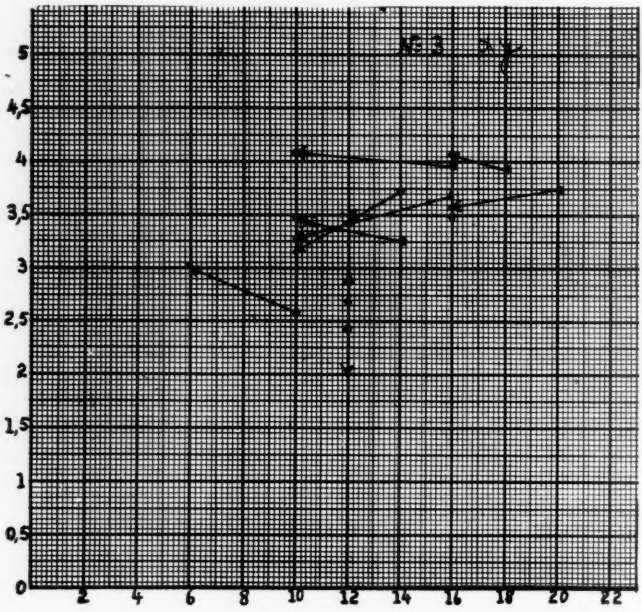


Graph 1. α Group: Pure allergic asthma.



Graph 2. γ Group: Unclassified asthma with bronchoinfection.

the basis of the data given in the Method, these have not been set forth, yet it can be stated that in delayed expiration, the duration of the illness is not so important as the frequency, intensity and duration of the attacks.



Graph 3. $\alpha\gamma$ Group: Pure allergic asthma with co-existing bronchial infection.

In Graphs No. 1 to 4, the ordinates show the vital capacity in litres and the abscissae the delayed expiration in seconds, of the different asthmatic types and of the group of non-asthmatic chronic affections, before and after nebulization with Isorrenin. The arrow indicates the deviation observed after the nebulization.

It can be seen that although the vital capacity did not always improve, the delay almost in every case diminished.

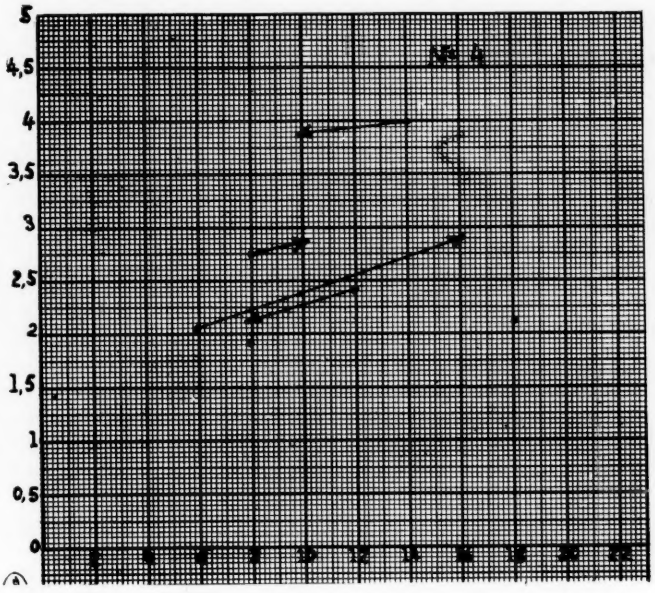
On analysing the graph No. 2, we see that although the vital capacity showed slight variations, after nebulization the delay decreased, but not as much as in the previous group. In other instances, when the vital capacity improved, there was an increase in the delayed expiration.

In the group with pure allergic asthma (Graph No. 3) there was little change in the vital capacity and delayed expiration.

The results shown in Graph No. 4 are similar to No. 3.

In Graph No. 5, as in all the previous ones, the vital capacity of all the types of patients pertaining to this paper, is shown in litres and the delayed expiration in seconds. An ideal curve has been added showing

the expiration time in relation to the volume of the vital capacity, as in theory, the expiration time in seconds is directly proportional to the amount of the vital capacity in litres. We consider that the normal area



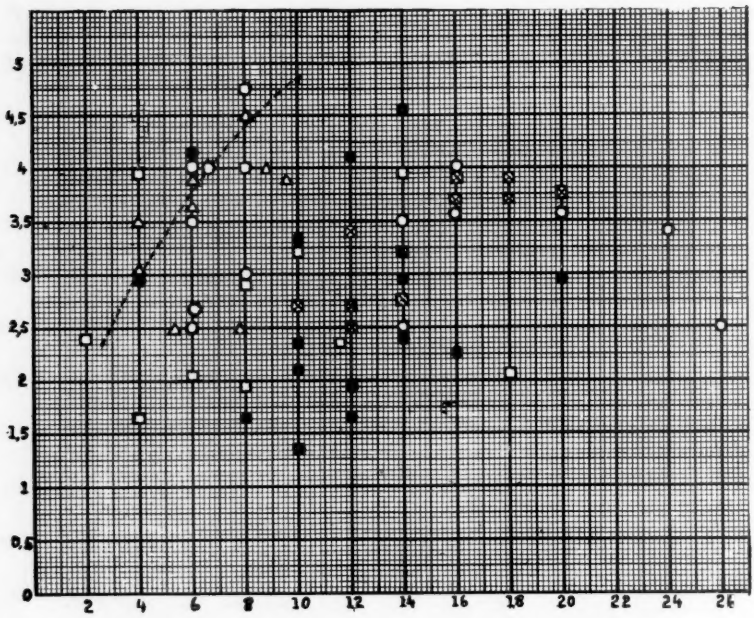
Graph 4. ω Group: Non-asthmatic respiratory infection.

is to be found to the left of the curve or within the curve itself, and that the abnormal values are to the right.

It will be noted that in all the groups of individuals under consideration, even in some apparently normal ones, an expiratory delay (D.E.S.), sometimes very marked, is present and that the delayed expiration time in seconds is not necessarily proportional to the vital capacity. On the other hand, and irrespective of their group, in the individuals with no delayed expiration, the expiration time is directly proportional to the vital capacity.

Finally, in Graph No. 6, as in all the previous ones, the vital capacity and delayed expiration are shown, but in relation (or not) to the appearance or disappearance of the symptoms by virtue of the medical treatment instituted, viz., in relation to the evolution of the malady. The direction of the arrow shows the results after the treatment.

In the patients of the alpha and gamma type, the delayed expirations became normal some time after treatment had started, to wit, as their condition improved. On the other hand, in the alpha-gamma and omega groups, in spite of a discreet subjective improvement due to the treatment, the D.E.S. improved only slightly or not at all.



Graph 5. ○—Pure allergic asthma.
●—Unclassified asthma with bronchoinfection.
⊠—Pure allergic asthma with co-existing bronchial infection.
□—Non-asthmatic respiratory infection.
△—Normal.

COMMENTS

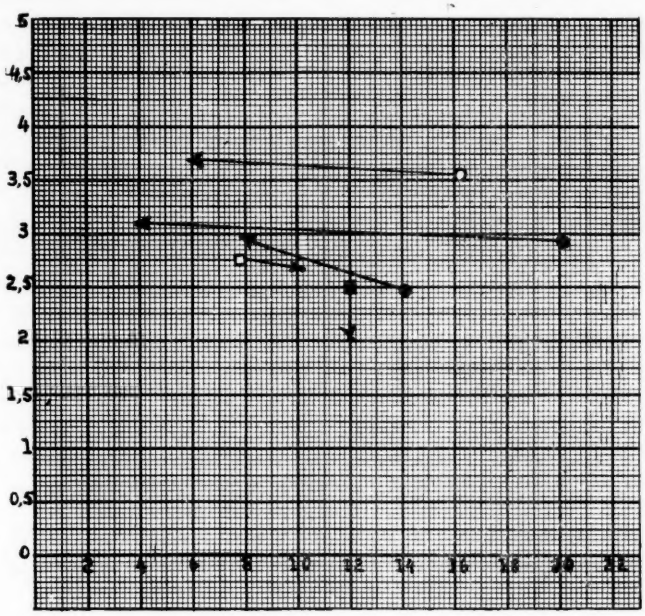
Before analysing the results, we wish to make it clear that we do not claim that the times obtained are very exact in the delayed expiration measurement: our only purpose was to be in possession of a simple method of measurement and comparison. Actually, more exact delayed expiration measurements can be obtained indirectly by means of methods which compare the expiratory time with the speed of the current of air such as the Hadorn pneumometer modified by Merkle and Wyss,[24] or those measuring time and volume of expired air according to Hamburger, Halpern and Degeorges[16] and finally, fractioning the vital capacity according to time (Gaensler[13]).

We also would like to point out that, although the delayed expiration has been determined in the air reserve, it has been in relation to the vital capacity and not actually with the latter, as the vital capacity variations are more illustrative and give clearer information on the results obtained.

This does not mean to say that the variations in the vital capacity show all the variations experienced by the types of disorders under consideration, because according to Gaensler,[14] (above all, in asthma and after the

bronchodilatory tests) the vital capacity does not reveal all the improvements obtained. Therefore, it is much better to determine the maximum respiratory capacity. But, broadly speaking, the vital capacity together with the delay time is sufficient for the practical requirements of this work.

On considering the results, it can be seen (Table I) that the patients, irrespective of the group to which they belong, had a respiratory delay frequently associated with the pulmonary auscultation signs and with



Graph 6. Groups: α (○), γ (●), αγ (⊠) and ω (□) (See text).

the subjective or effort dyspnea mentioned by the patients; these were never examined during an acute attack of asthma or dyspnea, but only during the intervals.

But this is not strange. According to many authors,[5,6,24] asthma patients, when not suffering an acute attack, have slight symptoms allied either to the concommitant emphysema or bronchitis, which are only discovered by functional studies of the lung.

It is of great interest that the delayed expiration often is not to be found in acute attacks of asthma. Herraiz Ballestero[17] in his cases, found it very seldom and in his comments on one of them, says: "the delay appeared paradoxically when the patient improved." Also when examining Herxheimer's spirograms[18] (who caused acute attacks of asthma

in sensitive subjects by nebulization with various pollens and allergens and then registered the results spirographically), the delayed expiration is not found in those tracings either.

As Herraiz Ballesteros[17] says, this apparent contradiction could be due to the fact that the mechanism of the acute attack of asthma is different to that of the slight symptoms complained of by the patients outside an attack. In fact Battro and Labourt[4] speak of von Basch's pulmonary rigidity as being due to the circulatory stasis and the consequent reduction in air supply to the lung, and Jiménez Díaz and Lopez García[21] maintain that during an attack of asthma there is ingurgitation of the small circle (described by von Basch) due to active congestion and to a certain degree of edema. Herraiz Ballestero[17] is of the same opinion, discriminating between congestive and obstructive asthma, the latter being the cause of the delay, that, according to Jiménez Díaz and Lopez García,[21] is due to diffuse bronchial occlusion caused by mucus, and which is different to the acute attack caused by active lung congestion.

Graphs No. 1 to 4 show that the delay in the alpha and gamma groups decreases after Isorrenin nebulization. Many authors[1,6,7,9,10,14,15,19,22,23,24] support the theory that, in these cases this phenomenon may be due to *bronchial* obstruction caused by spasm or mucosal edema and congestion.

On the other hand, in the graphs corresponding to the alpha-gamma and omega groups, the disappearance of the retardation does not take place or is very slight, after the bronchodilatory therapy. This, according to Christie[8] and others,[6,7,9,14] could be attributed to a pulmonary emphysema; others say it may be due to serious disorders of the bronchial mucosa with chronic infiltration (Knipping,[22] Anthony,[1] Cournand and Richards[10] and Merkle and Wyss.[24]

As regards the possible influence of Isorrenin nebulization on the pulmonary circulation (which would be improved by the consequent amelioration of the symptoms) we do not think it feasible as the amount of drug is too small and the time exposition too short. Moreover, and according to Dautrebande[12] and Merkle and Wyss,[24] the drug is not absorbed by the circulation, so that it can have no effect on it, but does influence the bronchial obstruction, especially that of the spasmodic type.

All these bronchial disorders can be followed perfectly by making a parallel study of the patients' sputum and of the spirograms. In this way the exaggerated mucorrhea, the bronchial desquamation, infection and infiltration, together with their alveolar repercussion, can be seen, disorders which, when repeated, can give rise to a chronic disorder of the bronchial mucosa, the subsequent emphysema and consequent loss of pulmonary elasticity. Particularly illustrative is the analysis made of two autopsies performed by Baldwin, Cournand and Richards[3] on asthmatics whom they had studied functionally in life, conclusions of which were later confirmed by pathological examination.

But the D.E.S. should not be taken as belonging exclusively to bronchial

disorders in asthmatics, as on examining Graphs No. 4 and 5, it appears also in other chronic alterations of the respiratory tract, such as multiple bronchiectasis, fibrosis with emphysema and emphysema due to non-asthmatic chronic bronchial diseases.

Also it does not indicate any given type of asthma, as it appears in all the types included in Ruiz Moreno's classification.[25]

But as Bercke et al[6] so rightly state, only one spirogram of the patient is not sufficient, even when carried out with a bronchodilator. It must be repeated several times with the same patient, at different stages in the evolution of the disease. In Graph No. 6 we see how in patients of different types, in whom there seemed to be an irreversible disorder because the delay which did not disappear with bronchodilatory medication, further tracing carried out after their condition had improved under treatment showed that the delay had completely or partly disappeared, thereby indicating that there was no irreducible emphysema.

Finally, as Comroe[9] says, functional examination, notwithstanding its great value, is not sufficient in itself for studying asthmatics, and radiological and laboratory tests are necessary and, above all, a good case history is required.

CONCLUSIONS

1. The study of spirograms makes it possible to discover the presence of the D.E.S. in many asthmatic patients, during periods of remission.
2. D.E.S. appears in all the types of asthma considered in this paper.
3. D.E.S. also appears in other chronic non-asthmatic disorders of the respiratory tract.
4. D.E.S. disappears or decreases after successive nebulizations with adrenalin derivatives. This seems to show that there is no irreversible pulmonary disorder in these cases.
5. To prove an irreversible broncho-pulmonary disorder, besides the bronchodilatory test, it is necessary to carry out several tracings during the course of the illness and to follow the evolution of the patient because the D.E.S. sometimes disappears in spirograms carried out, later without a previous bronchodilator treatment.
6. Apparently, delayed expiration is a sign of transient or permanent bronchial obstruction or a diminution of pulmonary elasticity.
7. The search for the D.E.S. in repeated spirographic studies of asthmatics enables us to obtain interesting data on the prognosis of the case.

SUMMARY

Spirographic tracings were made of sixty subjects: ten did not show clinically any disorders of the respiratory tract; ten had various non-asthmatic disorders (clinically) of the respiratory tract and the remaining forty had different types of asthma. In all of them spirographic tracings were carried out before and after nebulizations with a bronchodilator and in some new tracings were performed some time after the first.

In all cases the delayed expiration was calculated in seconds and it was possible to prove that the D.E.S. appears in any type of asthma and also in some non-asthmatic patients with emphysema.

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BACTERIAL ALLERGY IN THE RHEUMATIC DISEASES

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THE basic manifestations of the hypersensitive state are the result of an antigen-antibody reaction, whether it occurs *in vivo* or *in vitro*. When a union occurs in the living organism, a histamine-like substance is released which, in the main, is responsible for symptoms. When released suddenly, it may produce anaphylactic phenomena. *In vitro*, this union of antigen-antibody results in specific agglutinins or precipitins, and in the presence of complement, lysis of specific particulate antigens. Antibodies, essentially globulins, may be labile or fixed in the tissue. This distribution of humeral and cellular antibodies varies with animal species and type of antibody. For example, in the guinea pig antibodies to horse serum are largely attached to the cells, while in the rabbit they are of humeral distribution. The guinea pig, therefore, is selected when demonstrating anaphylaxis and the rabbit when producing diagnostic serums.

TWO TYPES OF ALLERGIC REACTIONS

Different antibodies show selective localizations in the several embryological cellular systems. This localization determines the site of greatest irritation when the specific antigen is injected into the organism. Antibodies of the various pollen antigens appear to be associated with the epithelial tissues. This association may be observed in the symptoms of hay fever, or demonstrated readily by skin tests. The antibodies of bacterial antigens do not appear to be attached to epithelial tissues. Local allergic reactions of the tuberculin type may be elicited with some bacterial antigens but are for the most part absent. Their slow development and the deep-seated fibrous involvements attending them seem to indicate that the irritation occurs primarily in white fibrous tissue. Bacterial antigens prepared from gram positively staining cocci, notably streptococci, produce no local reactions, or insignificant ones, upon intradermal injection. Instead, they produce or aggravate the general symptoms ordinarily associated with the rheumatic diseases—pain, swelling, and stiffness. The irritant following the injection of aqueous extracts of streptococci appears to be released in muscles, joints, tendons, and bursae. These extracts contain no coagulable protein, and only traces of organic nitrogen presumably that of proteoses and polypeptids. The implication is that these substances, acting as antigens, originate this set of symptoms by seeking out antibody attached to the cells of white fibrous tissue. The slow tuberculin-like type of allergic reaction results and contrasts sharply with the "flare" reaction following the intradermal injections of pollen antigens. Embryologically the "shock tissues" in the latter type of reac-

tion appear to be of epidermal origin; those of the tuberculin-like type of reaction, of mesodermal origin. The clinical procedures for desensitization in the two instances are governed by similar underlying principles but differ somewhat in their application.

A method of desensitizing patients who present rheumatic disease and are hypersensitive to streptococcal antigens has been developed.[12] The rationale of this treatment is predicated on the hypothesis that the rheumatic diseases are produced as a hypersensitive phenomena in tissues of mesodermal origin.

QUANTITATIVE RELATIONSHIP BETWEEN ANTIGEN AND ANTIBODY

Opie,[9] in 1923, showed that the irritating properties of the antigen-antibody complex are greatest when a large excess of antibody is present in the precipitate formed by the union of antigen and antibody in the test tube. The removal of the excess of antibody by thorough washing of the precipitate eliminated its irritating properties. If bacteria are injected as antigen, an amount of antibody approximately six hundred times as large[5] as the amount required to agglutinate the injected bacteria may be formed. Analytical methods using antigens labeled by isotopes, or by dyes, have demonstrated that the bulk of some of the antigen-antibody precipitates consists of antibody and only 2 or 3 per cent is formed by antigen.[6] Molecular ratios between antigen and antibody have been calculated in instances where the molecular weights of antigen and antibody are known. In specific precipitates of thyroglobulin-anti-thyroglobulin complex the ratio of sixty molecules of antibody to one of antigen appeared;[14] and in that formed by arsanilazoglobulin and its specific antiserum the ratio was fifty molecules of antibody to one of antigen.[3] Chemists are as yet without proof as to whether these combinations, topheavy with antibody, are held together chemically by valence bonds or whether nonspecific physical forces are responsible. Both may be factors since it has been shown that the ratio of antigen to antibody in the specific precipitates is affected both by the molecular size of the antigen[6] and by the relative amounts of antigen and antibody in the mixtures of the two when brought together for precipitation.[1,4,7] The importance for the allergist of these varying quantitative relationships centers about an apparent multiplicity of combinations of antigen and antibody, some of which may be irritating to the patient's tissues and some may not. The smaller doses of antigen may provide combinations with the antibody concentration in the organism which are highly irritating to the tissues, while larger doses yield combinations which are less irritating or non-irritating. This appears in tuberculin testing, where there is a well recognized range of dosage in which the reaction may be regarded as specific. Nelson[8] obtained positive reactions in proved tuberculous patients with as little as one-billionth of a milligram of PPD (purified protein derivative of Seibert)[11] but they could not be regularly regarded as specific with doses above one ten-thousandth of a milligram.

FOCAL INFECTION AND THE ALLERGIC STATE

It seems reasonable to assume that hypersensitiveness occurs in the presence of an excess of antibody, which may be produced and maintained by insignificant sources of antigen. This suggests that the bacterial allergies may be produced by a focus of infection too small to be regarded of clinical importance. Immunologically, it may furnish enough native antigen to hypersensitize the patient and maintain thereafter irritating amounts of an antigen-antibody complex. Choucroun[2] induced tuberculous allergy in all of fourteen humans by a single injection of 0.2 cc of paraffin oil containing two hundred gamma of each of two chemical constituents of the tubercle bacillus—a liposaccharide and a tuberculoprotein. The tuberculin tests, previously negative, were positive five weeks after the injection, and in one instance persisted for as long as twenty-seven months.

Hyposensitization by this concept would be induced by reducing the antibody-antigen ratio by fractional combinations of antibody with enough antigen to provide a complex which would be less irritating to the patient's tissues. The period through which a given dose of antigen would be effective in this respect would depend upon the time required to restore through biologic processes the former antibody-antigen ratio. Experiments with aminoacids containing N 15 have indicated that the "half life" of antibody globulin[10] is about fourteen days.

THE FACTOR OF TIME IN DESENSITIZATION WITH BACTERIAL ANTIGENS

The flare of the skin test in pollen allergy may be interpreted in either of two ways. It may be regarded as being due to histamine-like substance released throughout the process of the union of antigen and antibody. According to this view, the onset of the "flare" reaction would mark the beginning of the antigen-antibody reaction; its height, the consummation of it; and, its duration, the completion of it, plus the time required for the fading of the flare produced by the histamine released during the reaction. After the union is completed, the flare lasts only as long as one would last from an injection of preformed histamine. The entire flare reaction is short as compared with the period of clinical improvement following a single injection of antigen. This suggests the second interpretation, namely that the flare occurs only at the beginning of the interaction between antigen and antibody when the predominance of antibody is greatest, and the complex is most irritating. As the reaction continues the antibody combination takes on enough antigen to eliminate its irritating properties. The duration of the clinical improvement might be regarded as dependent upon the stability of this benign antigen-antibody combination. Since the period of clinical improvement lasts considerably longer than the flare of a single intradermal injection of antigen, the indication is that the antigen-antibody combination breaks down more slowly than it is formed, and that the duration of the period of clinical

improvement is a more reliable index by which to space doses of antigen in a course of treatment than is the "flare" reaction. This becomes especially important in bacterial allergies where the skin reaction is usually absent.

CUMULATIVE EFFECTS OF ANTIGENS

In our work with streptococcal antigens in the rheumatic diseases, we have noted cumulative effects, resulting eventually in overdosage, when the doses were spaced at fourteen days or less. Perennial treatments at intervals of twenty-eight days have not shown this, so that a given dose of antigen could be repeated month after month with consistent results. The shorter intervals were customarily used earliest in establishing a course of treatment. These cumulative effects with signs of overdosage appeared even though the injections were spaced to correspond to the termination of the periods of clinical improvement. This has been interpreted as an indication that the clinical symptoms begin to reappear before the antigen-antibody complex resulting from the previous injection of antigen has been entirely dissipated. Since intervals of twenty-eight days may be used without signs of cumulative effects, this interval has come to be regarded as the "life" of the antigen-antibody complex with full doses of the particular streptococcal antigen used in our work, and fourteen days as the "half life." This interval of fourteen days corresponds very closely to the interval of clinical improvement in patients who are responding well to treatment and in whom the dosage of antigen may be regarded as nearly optimal. For practical purposes in establishing a course of treatment with streptococcal antigen in rheumatic disease, the "half life" of any trial dose of antigen may be regarded as corresponding to the period of clinical improvement following its use. The small dose of antigen used at the beginning of a course of treatment does not ordinarily give a period of improvement of fourteen days' duration, but whatever its length, a second dose should be administered as soon as possible after the relapse which terminates it. This second dose has posed a problem for years because symptoms of overdosage frequently followed its injection. This difficulty has been largely eliminated since we have regarded the relapse as occurring at "half life," or 50 per cent utilization of the preceding dose.

In a former publication[13] the importance of volume dosage and constant percentage increments of it from dose to dose was emphasized. A constant percentage increment table of antigen dosage was presented in that publication. This table may now be supplemented to show the amounts of antigen to use in course at "half life" intervals, or clinical relapse time. These amounts are indicated in parentheses immediately following the constant percentage increment dose desired. It is interesting to note that these adjusted amounts of themselves constitute a series with constant percentage increments from dose to dose.

TABLE I. ANTIGEN DOSAGE AT HALF LIFE INTERVALS

Dilutions of Antigen*				
10^{-18} 10^{-13} 10^{-8} 10^{-3}	10^{-17} 10^{-12} 10^{-7} 10^{-2}	10^{-16} 10^{-11} 10^{-6} 10^{-1}	10^{-15} 10^{-10} 10^{-5}	10^{-14} 10^{-9} 10^{-4}
cc .10(07)	cc .11(08)	cc .12(08)	cc .14(10)	cc .15(10)
.16(11)	.18(12)	.20(14)	.22(15)	.24(16)
.26(18)	.29(20)	.32(22)	.36(24)	.39(26)
.42(29)	.47(32)	.52(36)	.58(39)	.63(42)
.68(47)	.76(52)	.84(58)	.94(63)	.—

*The antigen used in our treatment of the rheumatic diseases is an extract in normal saline of suspensions of non-hemolytic streptococci (S. cardioarthritidis).

Table I is applicable as long as progressive dose increases are used. If, however, it is desired to revert to a constant dose at any point in the series of injections, this may be done by administering one-half of the last available dose, which in the table always stands before the parenthesis enclosing the amount last injected.

After a constant dose at fourteen-day intervals is reached, the patient may gradually be brought under the perennial plan of treatment by using slightly larger doses of antigen at intervals of three to four weeks. In rheumatoid arthritis, it appears to be necessary to follow this plan throughout the patient's lifetime. The treatment may be maintained year after year without relapse serious enough to keep the patient from his usual employment. (Our record to date has been twenty-five years.) In rheumatic carditis from one to five years of treatment are ordinarily deemed necessary, but in rheumatic fibrositis shorter intervals of treatment are the rule. Several short articles are in preparation which will present in detail the clinical methods employed in fibrositis, osteoarthritis, rheumatic carditis and rheumatoid arthritis. It is hoped that they will serve to encourage clinical allergists to enter the tremendous new field represented by the rheumatic diseases.

SUMMARY

1. Two types of allergy and the quantitative relationships between antigen and antibody are presented.

2. The importance of considering the duration of the effects of single doses of streptococcal antigens as related to the intervals between doses in the desensitization treatment of the rheumatic diseases is discussed.

3. A table of dosage in the interest of greater accuracy is included.

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UNUSUAL TOXIC REACTIONS TO SULFONAMIDE AND ANTIBIOTIC THERAPY

A Review of the Literature from 1936-1953

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New York, New York

THIS paper reviews the literature from 1936 to November 1, 1950, concerning the unusual manifestations of toxicity which were described in case reports dealing specifically with toxic reactions observed during and after the systemic administration of the following antibacterial agents: aureomycin, bacitracin, Chloramphenicol,® dihydrostreptomycin, penicillin, streptomycin, sulfadiazine, sulfaguanidine, sulfamerazine, sulfanilamide, sulfapyridine, sulfasuxidine, sulfathalidine, sulfathiazole, terramycin, and tyrothricin (applied topically). The literature on aureomycin, Chloramphenicol,® neomycin, and terramycin from November 1, 1950, to January 1, 1953, is also reviewed.

Table I summarizes from over 700 individual case reports the unusual toxic reactions to the above-mentioned antibacterial agents. The total number of bibliographic references (included opposite each reaction) can be considered an indication of the minimum number of occurrences of this reaction reported individually.

This compilation was prepared as a part of a detailed comparative review of the reported toxicity of antibacterial drugs and is presented solely as an extensive survey of the literature, it not being possible nor the intention of the authors to draw conclusions or discuss the findings within the short confines of this paper.

Other aspects of the toxic reactions to antibacterial therapy have been reported in great detail in separate communications.[1,2]

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TABLE I. REVIEW OF THE LITERATURE OF THE UNUSUAL TOXIC REACTIONS TO ANTIBACTERIAL THERAPY DESCRIBED AS INDIVIDUAL CASE REPORTS.

Reaction	Bibliography Nos. of Case Reports
AUREOMYCIN	
Acne rosacea	1
Ageusia	2
Anal irritation	3
Angioneurotic edema	4-5
Anxiety	6
Bitter taste	7
Black tongue	8
Chest burning	9
Desquamation—oral	10
Eczematoid eruption	11
Edema	12
Emotional disturbance	13
Erythema multiforma	14
Genito-Urinary inflammation	15
Glossitis	16
Heartburn	17
Itching scalp	18
Laryngeal Stenosis	19
Local sensitization	20
Rash	21
Salivation	22
Sore Mouth	23
Tension	24
Urticaria	25
Vesicular eruption	26
Ulceration of muc. membr.	27
CHLOROMYCETIN	
Agranulocytopenia	28
Asthma	29
Bitter taste	30-31
Blurred vision	32
Cardiovascular collapse	33
Erythroid arrest	34
Giant urticaria	35
Granulocyte hypoplasia	36
Granulopenia	37
Hypothermia	38
Mental disturbance	39
Multiorificial dermatitis	40
Shock	41
Urticaria	42
Vesicular eruption—oral	43
PENICILLIN	
Acute eczema	44
Acute exfoliative dermatitis	45-49
Adhesions following intraperiton. applic.	50
Adhesive arachnoiditis	51
Agranulocytosis	52
Anaphylactic purpura	53
Anaphylactic shock	54-56
Anemia	57
Angioneurotic edema	58-59
Anuria	60
Arthritis	61
Arthus phenomenon	62
Asthma	63
Black tongue	64-69
Bronchial spasm	70
Bronchopneumonia from	71
Bullous dermatitis	72
Cardiac insufficiency	73
Cheilosis	74-75
Contact dermatitis	76-79
Cutaneous intolerance	80
Death	81-87
Delirium	88
Dermatitis venenata	89-91
Dermographia	92
Dyshydrotic exanthem	93-94
Embolism	95-99
Eosinophilia—Asympt.	100
Epilepsy after intraspinal Penicillin	101-102
Erythema—fixed	103-104
Erythematous eruption	105
Glossitis	106-109
Hemoglobinuric nephrosis	110
Hepatitis	111-112
Herxheimer reaction	113
Hypoglycemia	114
Hypoprothrombinemia	115
Jaundice	116
Meningitis	117
Metrorrhagias in pregnancy	118
Monilia infection from	119
Myocarditis	120
Necrosis after	121
Nicotinic acid deficiency	122
Ocular dermatitis	123
Oral desquamation	124-127
Oral hemorrhage	128-129
Paraplegia	130-131
Peripheral n. injury	132
Peripheral neuritis	133
Psychosis	134
Renal block	135
Schwartzman phenomenon	136
Serum sickness-like	137-143
Stomatitis	144-145
Swollen tongue	146-152
Thrombocytopenic purpura	153
Thrombosis	154
Urticaria	155-156
Vascular necrosis	157
Vesicular eruption	158-159

TABLE I. (Continued)

Reaction	Bibliography Nos. of Case Reports
STREPTOMYCIN	
Agranulocytosis	160-163
Amaurosis	164
Anaphylactic shock from	168
Aplastic anemia	166-168
Blindness	169
Bullous eruption	170
Cardiovascular disturbance	171
Contact dermatitis	172-182
Deafness—permanent	183
Death	184-188
Dermal sensitization	189
Dermatitis venenata	190
Digital gangrene	191
Eczema	192
Eczema of eyelid	193
Encephalitis	194-195
Encephalopathy	196-198
Epileptic seizure	199
Erythroderma	200-202
Exanthems	203
Exfoliative dermatitis	204-206
Glossitis	207
Granulopenia	208-209
Hemopoietic accidents	210
Hemorrhagic aleukemia	211
Hepatitis	212
Hypoprothrombinemia	213
Jaundice	214-215
Leukoplakia	216
Leukopenia	217
Macular eruption	218
Masking inflammation	219
Membrane formation—oral	220-221
Neurogenic tetany	222
Paralysis of vocal cord	223
Pruritus	224-225
Psychic disturbance	226
Purpura	227-229
Space and color perception disorder	230
Stomatitis	231-241
Thrombocytopenia	242
Ulceration—oral	243-246
Urticaria	247-248
Vesicular eruption—oral	249
Visual disturbance	250
DIHYDROSTREPTOMYCIN	
Oral paresthesia	251-252
Syncope	253
Ulceration—oral	254
SULFADIAZINE	
Acute hemolytic anemia	255-259
Acute mania	260
Agranulocytosis	261-268
Alkalosis	269
Anuria	270-284
Black tongue	285
Bullous dermatitis	286
Cheilosis	287
Cranio-cerebral nerve paralysis	288
Death	289-296
Desquamation—oral	297
Encephalopathy	298
Eruption—oral	299
Erythema multiforma	300-301
Exfoliative dermatitis	302
Fixed eruption	303
Fixed eruption of mucous membranes	304
Granulocytopenia	305-307
Hemorrhage—oral	308
Hepatitis	309
Hyperchloremia	310
Jaundice	311-312
Leukemia-like	313-314
Lupus erythematosus	315
Membrane formation—oral	316-317
Necrotizing arteritis	318
Necrotizing vascular lesions	319
Nephrosis	320
Oliguria	321-322
Oral blisters	323
Paresis	324
Passive transfer of sensitivity	325
Pemphigus-like reaction	326
Periarteritis	327
Plasmocytosis	328
Psychoses	329
Polyneuritis	330
Testicular atrophy	331
Thrombocytopenia	332-335
Ulceration—oral	336
SULFAGUANIDINE	
Anuria	337
Dermatitis	338
Morbilliform eruption	339
Nicotinamide deficiency	340
SULFAMERAZINE	
Anuria	341-343
Agranulocytosis	344-346
Death	347
Masking infection	348
Oliguria	349
Pemphigus-like	350
Purpura	351
Stomatitis	352
SULFANILAMIDE	
Acute hemolytic anemia	353-376
Agranulocytosis	377-391
Agraphia	392
Anuria	393-394
Auto-agglutination	395
Bullous eruption	396-398
Cerebral manifest.	399

TABLE I. (Continued)

Reaction	Bibliography Nos. of Case Reports
Death	400-412
Dermatitis	413-414
Dysmorphopsia	482
Eczema-photoallergic	415-418
Exfoliative dermatitis	419-420
Eye hemorrhage	421
Fixed eruption	422
Fixed erythema	423
Granulocytopenia	424-432
Hematuria	433
Hemorrhage—oral	434
Hepatitis	435-437
Hiccup	438
Jaundice	439
Leukemoid reaction	440-441
Leukocytosis	442-443
Methemoglobinemia	444
Motor aphasia	445
Myocardosis	446
Myopia	447-460
Necrosis of liver	461-463
Neutropenia	464
Optic neuritis	465
Pemphigus-like	466
Peripheral neuritis	467-468
Polyneuritis	469
Psychosis	470-473
Purpura	474
Purpura eruption	475
Renal anaphylaxis	476
Stammering	477
Transient nodal rhythm	478
Thrombocytopenic purpura	479
Varicelliform eruption	480-481
SULFAPYRIDINE	
Agranulocytosis	483-505
Anuria	506-539
Aplastic anemia	540
Arachnoido-radiculo-myelitis	541
Auto-agglutination	542-543
Cheilosis	544
Death	545-555
Erythema	556
Erythema nodosum	557-560
Erythematous eruption	561
Exanthema	562
Exfoliative dermatitis	563-566
Fixed bullous eruption	567
Granulocytopenia	568-572
Hematuria	573-581
Hemolytic anemia	582-587
Hemorrhage—oral	588-593
Hepatosplenomegaly	594
Hypersensitivity	595
Jaundice	596
Leukemoid reaction	597
Leukocytosis	598
Liver toxicity	599-600
Membrane formation—oral	601-603
Meningo-encephalitis intox.	604
Meningomyelitis	605-606
Myopia	607
Necrosis after injection	608-609
Necrotizing arteritis	610
Neuritis with wasting of smooth muscle	611
Neutropenia malignant	612
Papules—oral	613
Paralysis	614
Paraplegia	615-618
Pemphigus-like	619
Peripheral neuritis	620
Polyneuritis	621
Radiculo-neuritis	622
Stomatitis	623
Thrombocytopenic Purpura	624-633
Thrombosis	634-635
Ulceration—oral	636
Uremia	637
SULFASUXIDINE	
Agranulocytosis	638
Arthralgia	639
Dermatitis	640
Myalgia	641
Polyneuritis	642
Rash	643
SULFATHALIDINE	
Aching	644
Chill	645
Fever	646
Headache	647
Nausea	648
SULFATHIAZOLE	
Acute yellow atrophy	649
Agranulocytosis	650-656
Alopecia	657
Anaphylaxis	658
Angioneurotic edema	659-660
Anuria	661-662
Arthritis	663
Blindness—temporary	664
Bronchial asthma from	665-666
Conjunctivitis	667
Contact dermatitis	668
Death	669-676
Dermatitis	677
Dermatitis fixed	678-680
Dermatitis venenata	681
Epilepsy	682
Erythema multiforma	683
Erythema nodosum	684-689
Erythrocyte aplasia	690
Exfoliative dermatitis	691-694
Fixed eruption	695-696

TABLE I. (Continued)

Reaction	Bibliography Nos. of Case Reports
G. I. Hemorrhage	697
Glaucoma	698
Granulocytopenia	699
Hemolytic anemia-acute	700-703
Hemorrhage—oral	704-705
Hypersensitivity	706
Liver necrosis	707
Necrotizing arterial	708-709
Neuritis	710
Oliguria	711
Paresthesia	712
Periarteritis nodosa	713
Polyneuritis	714-715
Retinal hemorrhage	716
Rheumatism	717
Skin necrosis	718
Thrombocytopenic purpura	719-722
Thrombopenia	723
Varioliform eruption	724
Vesicular eruption	725
Vesicles—oral	726
TYROTHRICIN (TOPICAL APPLICATION)	
Burning sensation	727
Contact dermatitis	728-730
Delayed healing	731
Delirium	732
Dermatitis	733
Discomfort	734
Erythema	735
Headache	736
Hemolysis of r. b. c.	737
Hyperpyrexia	738-739
Itching	740-741
Local pain	742
Meningitis	743
Necrosis	744
Olefaction disturbance	745
Rash	746
Scaling	747
Slough	748
Soreness	749

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SUPPLEMENT TO TABLE I.

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NOVEMBER 10 IS THE DEADLINE

REPEATED INJECTIONS OF HORSE SERUM IN THE RABBIT

(Historical Document)

M. MAURICE ARTHUS

THE FACTS shown in this account will eventually be developed and analyzed; if I publish today an incomplete study, it still carries a lesson which should find application in human therapy.

If, in the rabbit one injects under the skin, into the peritoneum or in the veins, aseptic horse serum (experiments made with antitoxic sera), fresh or preserved, heated to 57 degrees or not heated, one does not produce any reaction, immediate or delayed. The horse serum is not toxic for the rabbit. If one repeats at intervals of several days, the injection of horse serum, one finds that after some injections, even in small doses, there is produced reactions which according to the degree of preparation of the animal, are mild or severe; which according to the route of introduction are local or general, immediate or delayed. Horse serum is toxic for the rabbit anaphylactized by and for horse serum. (The word anaphylaxis was proposed by Monsieurs Richet and Portier to designate the state of hypersensitivity to the poison of the tentacles of the actinae, produced in the dog by a first injection of this poison.)

A rabbit receives under the skin every six days 5 cc of horse serum. After the first three injections resorption occurs in several hours; after the fourth injection there is produced in the injection zone a soft infiltration which does not resolve for three to four days. After the fifth injection the infiltration which is produced is harder, edematous and does not resolve until after five or six days at least. After the sixth injection the edematous infiltration is transformed rapidly into a profound alteration of the subcutaneous, cellular tissue into a hard, compact, solid, white mass (absolutely aseptic and which is not pus) persisting for weeks, unaltered. After the seventh injection the same changes occur in accentuation; the skin which covers the diseased area becomes rapidly red, then blanches and becomes dry; an area of gangrene appears, the tissues of which disappear very slowly (several weeks) leaving a deep, ragged sore which cicatrizes very slowly. The general condition of the animal remains good. This is a typical experience; but it may be that the periods will be less clearly drawn; it may be that necrosis is produced before the seventh injection; it may be that the first reactions only appear after the fifth, sixth, or seventh injections.

These local phenomena are not the consequence of the repetition of the injections always in the same area. They are produced following a new injection, the first in the peritoneum and the new injection under the skin.

These phenomena are not the consequence of the accumulation of serum

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From the Transactions of the Society of Biology, Session of June 16, 1903. Translated from the original French by Marion T. Davidson, M.D.

in the rabbit organism or of the presence of a large quantity of the serum The same phenomena have been observed following the injection of 1 cc and even less, given at intervals of eight days, whereas injections of 10, 20 to 40 cc given at one single time, or repeated for several days, each day, have not produced the reaction. Noteworthy in passing, is that the profound changes in the cellular tissue and the area of gangrene are only produced following one injection under the skin of the thorax or abdomen; the injection made under the skin of the ear has produced only edema, fairly voluminous and long persistent.

If one injects 2 cc of horse serum in the ear vein of a rabbit which has been made anaphylactic by subcutaneous or intraperitoneal injections of horse serum, one stimulates reactions which according to the anaphylactic state of the animal, are fatal or not fatal, immediate and delayed.

When a rabbit which has been anaphylactized by six to eight injections of horse serum is given 2 cc of this serum in the ear vein, it shakes its head as if to sneeze after about a minute and then becomes anxious and agitated and finally lies down on its stomach; its respirations become polypneic but not dyspneic; the animal makes between 200 and 250 small, diaphragmatic, respiratory movements, without abnormal facial movements and without thoracic, respiratory movements. Fecal matter is evacuated in abundance. Finally the rabbit lies on its side, draws back its head, makes running movements with its feet and then becomes immobile and ceases to breathe. After a short pause during which exophthalmos appears (the corneal reflex is abolished), the rabbit makes four or five deep sighing movements and then becomes quiet. If the thoracic cage is opened quickly one finds the ventricles arrested in systole but the auricles still show some weak and spaced contractions. The blood is liquid throughout the circulatory apparatus. This ensemble of phenomena occurs in two to four minutes in general.

When a rabbit anaphylactized by four to five injections of horse serum is given 2 cc of serum in the ear vein it presents the first symptoms above described; pseudosneezing, anxiety, agitation, polypnea, fecal emissions; then all of these phenomena disappear rapidly (about a quarter of an hour). The animal apparently suddenly returns to normal. But some days later the same rabbit becomes cachectic, becomes emaciated with the skin appearing to be stretched over the skeleton. The hair becomes dry, brittle, prickly, falling in places and can be easily plucked out. The skin is flakey; the rabbit is generally inert, the eyes lusterless, the ear falls down; the ear is pale and transparent looking and an incision on its edge gives only a small drop of blood. The blood contains a considerable number of leukocytes but the red blood cells are diminished and the hemoglobin content is diminished. Often one sees areas of cutaneous necrosis and subcutaneous invasion, especially in the rump region. The rabbit dies in marasmus after several weeks without having shown any acute reactions.

One has observed in the guinea pig and in the rat, anaphylactic phenomena under the influence of repeated injections of horse serum. The phenomena observed in these animals will be described later.

One observes similar occurrences in the rabbit which has received several spaced injections of skimmed milk, sterilized at 110 degrees. The rabbit is anaphylactized by and for the milk just as it is by and for horse serum; the reactions are analagous to those produced in the case of serum. The rabbit anaphylactized by and for serum is not so for milk and vice versa. Experiments in preparation will tell us up to what point it is all right to generalize these results and if all albuminous liquids cause an anaphylactic state.

These experiments which were made during the last months of my stay at the Pasteur Institute of Lille, will soon be completed, developed and analyzed.

Will man show, under the influence of repeated injections of serum, an anaphylactic state and local or general reactions similar to those described for the rabbit? Information which has been furnished me from many sides (and many members of the Biologic Reunion of Marseilles have furnished me similarities to it following my communication) tend to establish that following a certain number (variable according to the subject under observation) of injections of therapeutic sera, given at several (eight to fifteen) days interval, one observes an edematous infiltration, more or less extended in the region of the injection. If these indications be confirmed by a methodical observation, one ought to admit that man is, like a rabbit, and in comparable conditions, anaphylactized by and for horse serum; and that anaphylactized man presents, like the rabbit, local reactions following subcutaneous injections, and will present similar constitutional reactions following intravenous injections.

These considerations should be kept in mind by those who will be making injections of horse serum repeated at intervals of several days for several weeks in order to be warned to caution. But nothing in these observed facts allows one to suppose that the practice of serotherapy is dangerous, such as is sanctioned by usage. Do not forget that anaphylaxis is developed only following several injections several times repeated and spaced several days apart. It does not develop in the rabbit before three to four weeks.

EDUCATION FILM GUIDE AVAILABLE

Educators Guide to Free Films—Mary F. Horkheimer and John W. Diffor, Eds.—Educators Progress Service, 13th ed., 516 p., paper, $6.00. This completely revised edition lists 2,574 films available free of charge, of which 562 are new additions to the listing.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

ALLERGY AND COMMUNITY HEALTH

A thought-provoking publication of the New York Academy of Medicine is reviewed in this issue. Its title, "The Epidemiology of Health" is indicative of the increasing preoccupation of modern medicine with the problems of prevention in a much wider sense than this term has been used in the past. The emphasis is on the community at large rather than on the individual. Thus the matter presented at the Academy's symposium comprised, in addition to the prevention of infective diseases, such factors of community health as environmental sanitation, nutritional habits and the psychology of intra-group cooperation. The increase in factual information is modifying our approach, as epitomized by the following quotation from one of the contributors to the symposium, R. I. Lee: ". . . the practice of medicine . . . has changed much and is now in the throes of further active change. . . . Once we looked at the end results of disease. Now we are looking at the earliest evidence of disease. We talk in terms of correctible defects. . . ."

When reading this book, this writer was struck by the fact, that hardly any of the contributors was aware of the large contribution, that the discipline of allergy has made to the armamentarium for the promotion of community health. In learning and teaching how to recognize the agents of sensitization in our surroundings, the allergist learns and teaches how to heal as well as how to prevent by avoidance or elimination. Witness our contributions to industrial health by pointing out and teaching how to avoid the sensitizing agents, with which industrial workers come into contact, and the similar service rendered the public at large concerning sensitizing agents in our daily surroundings, in the home and outside, in utensils, clothing, food, and last, but not least, in drugs. Indeed, services of this kind are the most soul satisfying ones within the scope of our specialty. And we can rightfully claim full membership in the team of the "epidemiologists" of health.—A.J.W.

Progress in Allergy

GASTROINTESTINAL ALLERGY

ORVAL R. WITHERS, M.D.
Kansas City, Missouri

HISTORICAL CONSIDERATION

According to Osler,[79] Willan[133] in 1808 was the first to publish a case of purpura associated with abdominal symptoms such as excruciating pain in the bowels together with anasarcous swelling of the legs, thighs and hands.

In 1868, Henry H. Salter[121] reported a case of gastrointestinal disturbance due to food in an asthmatic patient who was sensitive to milk.

Henoch in 1868[55] and again in 1874[54] emphasized the association of gastrointestinal symptoms with purpura and attempted to demonstrate a clinical entity.

As early as 1881, Jonathan Hutchinson[59] described cases with vomiting and a sense of sinking and abdominal distress, sometimes of such severity as to lead to the suspicion of poison. This was due, he believed, to the ingestion of eggs, as the symptoms disappeared when no eggs were eaten. He observed that these symptoms occurred even when this food was taken in the smallest amounts, as in puddings or soups. He also stated that honey, various fruits and vegetables, fish, tea, coffee and alcoholic beverages produced characteristic abdominal symptoms in certain individuals. Since then, from time to time, cases have been reported especially among children, who could tolerate neither milk nor eggs. These cases were described as "clinical entities," since there was no other satisfactory explanation at that time.

Osler[76] in 1888 stated that he thought the skin manifestations, such as erythema, urticaria, angioneurotic edema, purpura with abdominal crisis and arthritis pains, were all the result of a single pathological process.

In 1895, Osler[77] described a group of eleven patients with nephritis, purpura, arthritis, urticaria, angioneurotic edema, who in addition had gastrointestinal symptoms. A large portion of these patients had suffered from abdominal colic with occasional vomiting and diarrhea. He commented that the anatomical conditions associated with visceral symptoms were not well understood but that the changes in the gastrointestinal canal at least were probably the counterpart of what appears in the skin; namely, exudation of serum, swelling, hemorrhages and in rare instances, necrosis. At autopsy the hemorrhages have been found in the internal organs. He noted that the respiratory organs were less frequently involved. However, in one case the recurring attacks of cough with bronchitis he thought was part of the affection.

The discovery of anaphylaxis by Richet and Portier in 1902 was not followed immediately by the fact that food idiosyncrasy could be explained on that basis. It was not until 1906 that Wolff-Eisner suggested that hay fever might be an allergic phenomenon. This was the first mention of a possible correlation between experimental anaphylaxis and spontaneous clinical disease. It was in 1910 that Doerr suggested a common basis for food idiosyncrasy and anaphylaxis. Vaughan found it especially

interesting to learn that Doerr and Richet, two early students of anaphylaxis, each were sensitive to egg. Eight years appears to have elapsed following Richet's pioneer discovery before either of them realized that their own maladies might be due to a similar mechanism.[93]

In 1904, Osler[78] discussed the visceral manifestations of the erythema group of skin diseases and he commented that "the most constant feature in the whole group, occurring in twenty-five out of twenty-nine cases, was the recurring attacks of colicky pain sometimes with or without diarrhea and occasionally with the passage of blood." He also commented, in discussing angioneurotic edema of the bowel, "that the possibility of mistaking visceral crisis for appendicitis intussusception or obstruction of the bowel and handing the patient over to the surgeon is by no means remote.

Holtzknecht,[58] in 1906, was the first to report observed roentgenological changes in the gastrointestinal tract including spasm of the pyloric antrum, which was the result of antigenic food, according to Fries.[42]

Smith[113] reported some very interesting cases of gastrointestinal reactions due to buckwheat which occurred both in animal and man. Since gastrointestinal allergy was not known in 1909, the reaction was reported as buckwheat poisoning. Smith noted that the worst cases of buckwheat poisoning were seen in animals that were fed the buckwheat plant while in bloom, but that it also occurred after eating the grains, bran, chaff, straw or even the stubble. He described the symptoms as the severest of itching and swelling, especially of the skin around the face. At times it was so marked as to cause the eye lids to close and the ears to hang down. There were also present anorexia, retching, fever, dyspnea, cough and at times acute gastrointestinal disturbances such as diarrhea and retching.

Smith recorded the following symptoms of buckwheat sensitivity in a man who had been extremely sensitive to this product all his life. The patient reported "when buckwheat was first eaten I experienced a great discomfort in my throat, gullet and stomach. I felt as though I had swallowed hot lead. My face, eyes, tongue, neck, shoulders and hands were hot, inflamed and swollen, and my lips were thick with hives. Itching in these regions was unbearable. There was also extreme itching and burning of the mouth and always some drooling occurred. I could not swallow another mouthful of the cake nor endure the retching caused by what I had already eaten. Severe nausea and vomiting always occurred. My salivary glands were so susceptible to buckwheat that I can readily detect buckwheat adulteration in food by simply holding a portion of the suspected morsel under my tongue. If there is buckwheat adulteration my tongue swells and burns and there is a prompt increase in the flow of saliva, and it is needless to add, that since I have known the usefulness of this precaution no particle of food has been swallowed that showed the presence of buckwheat contamination. All nuts, except almonds and Brazil nuts affect me in a manner somewhat similar to buckwheat, except the salivary glands are not nearly so sensitive, nor is the effect on the lining of the stomach so immediate or severe."

Schloss is the author of several articles discussing alimentary disturbances in children. The first article was entitled "A case of allergy to common foods" and was published in 1912[109] Owing to the severe and at times alarming symptoms produced by ingestion he preferred cutaneous tests on the basis of vonPirquet's tuberculin test. The "borer" devised by von Pirquet was used to produce a uniform abrasion of the skin

and the test substances, egg, almond, oatmeal all produced a typical itching wheal with erythema at the site of abrasion. The stronger dilutions produced typical urticarial wheals by mere contact with the unbroken skin. Several tests were done to show that the skin reactions were due to the tested food and was specific and were not due to the various chemicals or to mechanical irritation. The test, of course, demonstrated conclusively that only the food substances to which the patient was extremely sensitive showed a positive reaction.

According to Schloss' report a child was first given the white of an egg in barley water when he was ten days old and no symptoms resulted. At fourteen months egg was given again and the characteristic symptoms of intolerance appeared. The baby took only a few tastes, cried, and refused more. Almost immediately he began to claw at his mouth and the tongue and buccal tissues swelled until they reached a size many times greater than normal. Toward the end of the second year he would frequently play with empty egg shells, which always gave rise to an urticaria rash over the hands and arms. When two years old, it was decided to determine the exact effect of egg, so he was given a small quantity of partially coagulated egg white between slices of bread. Only a small amount was swallowed and almost immediately he began to gag and vomit profusely. The child became extremely ill. He soon fell into a restless sleep from which he awoke in a few moments and vomited several times. Clinical reactions to almonds and oatmeal were similar to egg but not nearly so severe.

In 1914 Osler[79] again suggested the similarity between a condition that was exhibited by patients who suffered from hypersensitiveness to shell fish or from hay fever. He also suggested that serum rashes might belong to the conditions just described and felt that these patients might well be presenting the anaphylactic phenomena. It is interesting to note that in 1914 allergy as a clinical entity was just becoming established. Yet, he remarked in his last article on the subject that perhaps anaphylaxis was the key that would unlock the mystery of these cases.

X-ray studies started in this field when Crispin,[30] in 1915, first observed the appearance of angioneurotic edema of the pylorus by x-ray. He reported a case with gastric trouble for twenty-three years. This patient had a recognized angioneurotic edema, but in addition, the abdominal symptoms were severe pain and vomiting of large amounts of blood. Roentgen examination of the stomach just preceding an attack of angioneurotic edema showed a lesion of the stomach at or near the pylorus. Though the angioneurotic edema condition was recognized, exploratory laparotomy was advised because of the hematemesis and the x-ray findings. At operation, no lesion of the stomach was found and it was thought that the lesion reported by the roentgenologist was a visceral swelling similar to angioneurotic edema that appeared on the skin.

In 1917, Cooke mentioned that next to hay fever, gastrointestinal symptoms were the most common results of allergy.

Laroche, Richet and Saint Girons,[64] wrote in 1919 that acute abdominal pain is sometimes a permanent symptom of acute food allergy. This condition was described as, "grande anaphylaxie alimentaire." This condition is characterized by severe diarrhea and shock-like symptoms, in addition to the violent paroxysms of intense abdominal pain.

Spasm and obstruction of the pylorus and gastric retention were observed on the roentgenograms of food sensitivity in patients, by Wiedemann[132] in 1921.

Food allergy as a cause of abdominal pain was reported by Duke[36] in 1921. He wrote that he wished to emphasize the concise fact that a reaction caused by hypersensitiveness to a food could give rise to severe abdominal pain, and that that pain may be the prominent and often the sole striking manifestation of the reaction. He suggested that the abdominal symptoms of the reaction may be very violent, and could easily be mistaken for those caused by a serious abdominal lesion. He noted that in the majority of the cases pain appeared soon after ingestion of the food and lasted from three to six hours. In several cases, however, he noted that it did not appear for from three to twenty-four hours, and in these cases it lasted much longer. In the majority of his cases he observed that the pain was associated with nausea and vomiting and less frequently with indigestion, usually bloating, diarrhea, and mucus coated stools, and much less frequently with hives, angioneurotic edema and purpura. It is interesting to note that among the patients having food allergy that were reported by Duke, nearly 50 per cent had demonstrable pathologic lesions in the alimentary tract or in its appendages.

The fact that food allergy may cause pain in the upper right quadrant has now been recognized by many observers. One of the first to report that food allergy may be responsible for gall-bladder colic was Parturier[80] in 1924 according to Walzer et al.[128]

Andresen,[7] in 1925 showed the importance of food allergy as a cause of pain in the gall bladder and in the gastrointestinal tract.

Van Leeuwen[123] in his book *Allergic Diseases*, published in 1925, mentions vomiting and diarrhea as being the gastrointestinal symptoms produced by hypersensitiveness to foods. He quotes Laroche, Richet and Saint Girons who have recognized conditions which they designate as "la grande anaphylaxie alimentaire" and "la petite anaphylaxie alimentaire." The former is responsible for extremely serious symptoms leading at times to the cases of death in babies and adults from the ingestion of very small amounts of milk, egg or other foods; the latter, which is much more frequent, causing conjunctivitis, eczema, intestinal symptoms, rhinorrhea and attacks of asthma or migraine.

Although Osler was the first to suggest that purpura together with an erythematous group of skin lesions might be due to allergy, little was done to determine the soundness of this theory until Alexander and Eyermann[3] presented several cases of purpura in which allergy was determined to be the etiologic factor. The first cases of Henoch's purpura in which food was suggested as an etiologic factor were reported by these observers in 1927. They commented then on the similarity of many of the factors related to both Henoch's purpura and food allergy and suggested that the clinical characteristics were so striking that identity in their origin may be reasonably inferred. For example, a history of previous allergic symptoms, incrimination of particular foods as a cause of attacks, the identity of skin lesions, and the similar expressions of recurrent abdominal pain, and finally the identification of the same gastrointestinal lesions in each would tend to show that their fundamental etiologic causes and mechanism were the same.

In 1927, Rolleston[94] wrote, "It is well to remember that all dyspepsias are not surgical and that some are due to hypersensitiveness—the gall-bladder may be incited to spasm and so cause pain, thus imitating a gross organic lesion, such as calculus or cholecystitis—it is indeed possible that a change similar to urticaria may occur in the stomach and intestines."

Eyermann,[39] in 1927, reported on colonic manifestations of food allergy.

He published the first report on the effect of deliberate feeding of an allergenic food on the function of the gastrointestinal tract. His patient experienced symptoms similar to gall-bladder disease following the ingestion of whole wheat bread. Pain in the right upper quadrant as well as the spasm noted in the right flexure of the colon by x-ray vanished following the hypodermic administration of adrenalin.

Possibly the results of their great clinical experience and Eyermann's and other reports on pain in the upper right quadrant, led Graham, Cole et al,[48] in 1928, to write in their text *Diseases of the Gall Bladder* under the differential diagnosis as follows: "The conditions which are likely to be mistaken for chronic cholecystitis are numerous. One which is rather frequently confused with chronic gall bladder disèase is that of intestinal allergy."

Vaughan[124] wrote extensively on food allergy and in 1928 he published a report on the allergic factors in mucous colitis.

In 1931, Rowe,[102] summarized the works of previous authors and also reviewed the results of his own studies in 100 patients with gastrointestintal allergy in his book of food allergy.

During the past twenty-five years with the development of the subject of allergy a number of excellent articles and case reports of gastrointestinal allergy have appeared in the literature. Yet, in spite of this literature the importance of including allergy in the differential diagnosis of patients with atypical acute or chronic gastrointestinal disorders has not occurred to some physicians. Possibly this results from a low incidence of this ailment in the general population, as suggested by Squier.[115]

INCIDENCE

Squier[115] reviewed the incidence of symptoms which might be attributed to gastrointestinal allergy in one thousand consecutive private patients. The histories and complete allergic studies were made by the same two physicians. Almost all of the patients included in this series were seen presumably for some allergic disorder, so it was naturally expected that gastrointestinal allergy would occur more frequently than in a similar number of the usual group of medical patients. This investigator found that chronic gastrointestinal symptoms were recorded for only twenty-eight patients and that a diagnosis of allergy of the alimentary tract was actually justified in only seven of this group of one thousand allergic patients. He explained that this surprisingly low incidence would be slightly increased if he included the history of past acute gastrointestinal allergic reaction in this series. He explained that in infancy and early childhood the barrier of the gastrointestinal mucosa against the penetration of ingested protein is less effective than in later years. Therefore, symptoms of acute gastrointestinal allergy are more common during the early childhood than in later life.

He emphasized that the low incidence of gastrointestinal allergy in this series of allergic patients must not be interpreted as evidence that allergy may not be a potent cause of acute digestive symptoms. Rather this series points out that in a fairly large group of allergic individuals chronic gastrointestinal allergy was not found to be a frequent cause of symptoms. He suggested that patients with chronic gastrointestinal allergy are inclined to incriminate the last food eaten as the cause of their distress. As a result food suspicions mount and the list of foods to be avoided becomes progressively longer and longer. This author also called attention to a not uncommon practice of having a technician do the skin tests, and then, without consideration of the inadequacies and limitations of such

tests, hand the patient a food list with plus marks as a guide to the degree of avoidance necessary. This documentary evidence of "sensitivity" to foods, most or all of which were previously taken without the slightest distress, is often used by the patient as a criterion for additional food eliminations. Sometimes the symptoms of malnutrition may be added to those of pseudo-gastrointestinal allergy. Squier concluded that the diagnosis of gastrointestinal allergy is difficult and that although there is a general acceptance in the instance of acute gastrointestinal allergy there is a wide divergent opinion concerning the frequency of allergy as a cause of chronic indigestion, diarrhea and a multitude of other nondescript digestive symptoms and complaints.

Rowe[102] wrote in his monograph in 1931 "all of these facts . . . make me feel that gastrointestinal food allergy is a common and unusually overlooked cause of many mild and obscure as well as moderate and severe symptoms of this type."

In 1941 the same author stated, "Gastrointestinal allergy is much more common than is usually appreciated. He felt that it is frequent in infancy and childhood and is responsible for colic, pylorospasm, nausea, vomiting, regurgitation, cyclic disturbances, abdominal pain, diarrhea, mucous stools, constipation and other general symptoms which go unrecognized by the practitioner."[101]

In 1947 Cooke[29] wrote that, there was no available data on the frequency of gastrointestinal allergy. Although much has been written on the subject a critical examination reveals the fact that while allergy might properly be suspected as a cause of symptoms in a number of cases, there have been rather few in which the proof could be substantiated. He continued, and the reviewer considered it important that he be quoted verbatim:

"My own experience leads me to state the frequency in this way; acute gastrointestinal symptoms, with or without systemic evidences (urticaria, asthma), from allergic lesions reasonably assumed to exist in the tract are unusual but not rare. They occur in patients with immediate reactions following ingestion of food or drug allergens and also, though rarely, as part of the constitutional reaction from over doses of pollen and inhalant allergens. But these are not the cases that constitute the problem of the physician as a rule, for patients themselves are aware of these immediately reacting allergens and avoid them. Cases proven to be allergic, having had persistent or recurring gastrointestinal symptoms that constitute the primary reason for seeking medical advice, are not, in my opinion, common and certainly not as common as might be inferred from the literature on allergy. Nor are they readily solved as a result of study from a standpoint of allergy."

Feinberg[40] stated:

"Our experience indicates that the various allergic symptoms in the digestive tract combined to form a formidable total of allergic illness. The importance of gastrointestinal allergy has not been fully appreciated by most allergists. It is only recently that increasing attention has been given to it. Two major reasons have been operative in hindering interest in and awareness of this group of allergic manifestations. Many functional and organic digestive diseases present symptoms which are almost identical with those of allergy. The low incidence of positive skin reactions of gastrointestinal allergy has discouraged many and created skepticism in others. We have noted, for example, that very few patients with gastrointestinal allergy are referred by physicians or consult us for those complaints. But our observation of patients with other atopies indicates that many of the gastrointestinal complaints, previously labeled as functional colitis, peptic ulcer or cholecystitis, are of an allergic nature."

Rackemann[86] wrote that "allergy which is manifested solely or chiefly by gastrointestinal symptoms is very unusual."

Andresen[6] in 1951 stated:

"In my personal experience nearly 20 per cent of patients with gastrointestinal complaints were having some kind of allergic reactions and in 11 per cent of all such patients the principal symptoms were definitely allergic in origin. Thirty per cent of the latter group had been operated upon, often unnecessarily, as evidenced by the fact that their symptoms had persisted after operation and were promptly relieved when their allergic cause was discovered. Most symptoms for which no organic cause could be determined and which have been attributed to nervous indigestion, psychiatric and endocrine disturbances, can be demonstrated to be due to allergy. One of the reasons for the present craze for so-called psychosomatic medicine is undoubtedly the neglect of careful evaluation of allergic factors. It is now generally recognized that of all the manifestations of allergy, those in the gastrointestinal tract are the most common. In searching for the cause of gastrointestinal symptoms allergy must always be borne in mind. It is failure to consider allergy that accounts for so many mistakes in diagnosis and therapy."

ETIOLOGY

The most common causes of allergy of the gastrointestinal tract are foods and drugs. However symptoms have resulted from inhalants, contactants and the parenteral administration of therapeutic or prophylactic extracts and serums. And finally there are on record allergic reactions in the alimentary tract following the bite of insects.

Foods, naturally, are the most frequent offenders. While any food may be a cause, Cooke[29] states "the important ones are milk, egg white, egg yolks, chocolate, fish, shell fish, nuts, cottonseed, celery, peas, corn, sweet potato, pork, chicken, buckwheat and honey. I take exception to the importance of wheat and cereals as frequent causes, even in those who have positive wheals."

A patient with recurring attacks of abdominal discomfort simulating appendicitis was reported by Black.[14] The symptoms could be reproduced at will whenever the patient ate squash or cabbage.

Andresen[6] examined a patient once who presented the picture of carcinoma of the esophagus. The lesion was due to an allergic reaction to his chewing tobacco.

Ratner[87] reported definite allergic abdominal pain resulting from the use of pollens given orally for desensitization and orally administered vaccines. Abdominal allergic episodes may also result from any highly antigenic substance, such as endocrine products or other organic medications. This holds true for drug sensitivities to such substances as acetylsalicylic acid, bromides, sulfonamides and quinine, and many others.

Abdominal pain of allergic origin may be caused by a variety of specific reactions according to Fromer.[44] He describes a patient with violent lower abdominal pain as a part of a constitutional reaction from the hypodermic administration of pollen extract for the treatment of hay fever. Another of his patients experienced an anaphylactoid condition that followed the bite of a black widow spider. The generalized urticaria or angioneurotic edema was usually accompanied by shock-like conditions associated with excruciating generalized abdominal pain and a rigid abdomen.

Freeman[41] stated that pollen experimentally swallowed with food gave rise to nausea, vomiting, indigestion and diarrhea in some of his hay fever patients.

Jackson[60] saw an eighteen-year-old boy who had a complete obstruction of the esophagus four days after the injection of a prophylactic dose of diphtheritic antitoxin. The tongue was enormously swollen and he was drooling saliva. There was no difficulty in breathing. The x-ray examination showed complete closure of the esophagus at the level of the top of the arch of the aorta. The esophagoscope exposed a normal larynx and hypopharynx. A few centimeters below the beginning of the thoracic esophagus the lumen was completely closed by extremely firm, white, nodular masses that seemed to be part of the esophageal wall. A second esophagoscopy ten days later revealed a normal esophagus.

Gastrointestinal allergy occurring in a woman, aged fifty-two years, who had taken insulin for diabetes constantly for six years was observed by Williams.[134] The initial symptoms were cramps followed by frequent bowel movements. After two months had lapsed there was edema of the upper eyelids which occurred almost daily without relief despite treatment. In the meantime the gastrointestinal symptoms had increased in frequency and severity. When the patient changed from using insulin of pork origin to that of beef origin the cramps and diarrhea stopped almost immediately. Skin test of pork insulin resulted in a severe local reaction which persisted for twenty-four hours. During that time the intestinal symptoms reappeared. Skin tests of beef insulin were negative and the patient's symptoms were reproduced later by the administration of pork insulin.

Serum sickness simulating an acute abdominal disorder was reported by Derbes and Bruno[32] in a seventeen-year-old colored boy, who was admitted to the observation ward because of severe abdominal pain of two hours duration. There was no nausea, vomiting nor loose stools and no previous history of indigestion. Physical examination revealed generalized rigidity of the abdomen and the temperature was 100°F. There were 9,500 white blood cells, 91 per cent neutrophiles, and 9 per cent small monocytes. The urine was negative. The possibility of a perforated viscus was ruled out by x-ray. The pain was so excruciating that 1/6 gr. morphine had to be administered the second time to relieve apprehension, and severe discomfort. The patient was prepared for operation and kept in the observation room overnight. At seven o'clock in the morning it was noticed that there was a generalized urticaria associated with marked itching. The history then revealed that antitetanic serum for dog bite was administered three days previously.

Andresen[6] has seen attacks of diarrhea and even ulcerative colitis which occurred during hay fever season, due to pollen allergy. Sensitivity to some chemical constituent of "smog" or dusting powder has caused gastrointestinal symptoms. He observed a patient who had attacks of vertigo and vomiting after smelling a certain perfume. Allergic reactions in the alimentary tract have also resulted from the absorption of cosmetics or medications applied to lips, nose, mouth, anal region or other orifices and perhaps even to the unbroken skin. He reported one patient who experienced persistent vomiting whenever a particular brand of lipstick or dentifrice was used.

Wise and Sulzberger[135] observed an arsphenamine hypersensitiveness in a young nurse, with dermatitis, asthma, and severe appendicitis-like pains; these symptoms appeared only once weekly, that is on the day in which she prepared and therefore contacted arsphenamine solutions.

This reviewer felt that the few cases with varied etiology presented are sufficient to demonstrate that all gastrointestinal allergy is not necessarily due to ingestants, although it is the most common cause.

There are no characteristic symptoms of allergy of the alimentary tract since similar symptoms can be and more often are due to other causes. However, pain, nausea, vomiting and diarrhea (all in various combinations) are frequently observed.

Abdominal pain in children at times presents difficulty in diagnosis. Ratner[87] called attention to the fact that yearly children are subjected to many tests in the hospital to rule out tuberculosis, abdominal lymph nodes, various anatomic defects of the gastrointestinal tract, recurrent appendicitis, pyelitis, et cetera, and in many instances they are sent home with their ailments undiagnosed. This author was of the opinion that in some of these children the abdominal pain may have been due to food allergy. He suggested that Schloss[108] was one of the first to place certain cases of abdominal pain in the category of allergy. Cases of gastrointestinal allergy without positive cutaneous reactions were described. These infants regularly developed diarrhea, abdominal pain and vomiting when the smallest amounts of raw whole milk were ingested. Moderate amounts of thoroughly boiled milk were tolerated. Ratner reported his observation of a pair of twins in which the abdominal allergy was present without the confirmatory evidence of a positive skin test. When these infants were given a raw milk formula, one developed urticaria and the other developed abdominal pain, vomiting and diarrhea. Allergic skin tests proved positive to lactalbumin and whole milk only in the infant who developed urticaria; no skin reaction was obtained in the other infant who had gastrointestinal symptoms. Frequent clinical exposures to milk proved his observations to be correct. He concluded that it was a common experience that local organ sensitivity might precede a generalized sensitivity when certain tissues of the body (e.g., the intestinal tract in this instance) may be sensitive while others (e.g., the skin) were not. Ratner further suggested that in the diagnosis of abdominal allergy, pain of an allergic origin should always be ruled out whenever abdominal symptoms were present. He classified allergic abdominal pain in three groups: (1) Abdominal pain as a minor symptom in which it appears with or without an acute attack of urticaria or asthma and usually was of little or no significance. Many children complain of this symptom in the course of their asthmatic or urticarial attack. (2) Recurrent abdominal pain. This is the most frequent in children. Many cases give a history of colic and vomiting during infancy. Pain is usually localized in the region of the umbilicus but may also be present in the epigastrium, the paraumbilical region or the right lower quadrant. It is cramplike in character and may last for several minutes or hours and may recur at frequent intervals. As a rule, there are associated gastrointestinal symptoms such as diarrhea, flatulence, mucous stools, nausea, vomiting or even constipation. These symptoms usually follow the ingestion of some particular food. Fever as a rule is absent but on occasion may be present. Localized tenderness may be present during the attack but is frequently absent. (3) Severe abdominal pain simulating an acute surgical condition of the abdomen. Ratner emphasized that before surgical condition of the abdomen could be considered, it is important to review the following points favoring allergy: (a) a previous history of gastrointestinal symptoms, or food sensitivities; (b) a history of other forms of allergy; (c) the presence of eosinophilia; and (d) severe abdominal pain with physical signs that are atypical or negative. This author was of the opinion that an allergic abdominal disturbance may actually

lead to a surgical condition of the abdomen. So, even in the face of an allergic background, if the signs resemble appendicitis or intussusception surgical intervention may become imperative.

The complaint of abdominal pain in children is a subjective symptom and demands careful analysis of many factors before one makes a final diagnosis, especially the diagnosis of abdominal pain due to allergy commented Greenebaum[51] in discussing Ratner's paper. He continued that in confirming Ratner's allusion to the pathologic sequels of frequent allergic abdominal attacks, and he was permitted by Philip Wasserman, the pathologist of the Jewish Hospital of Cincinnati, to refer to some unpublished data. Wasserman collected a series of surgical cases of gall bladder and appendix infections, the microscopic examination of which showed allergic reactions consisting of edema, plasma cells, and great cellular response of eosinophils in place of the usual polymorphonuclear cells. These happened to be adults. Subsequent investigations reveal that food allergies were prominent in the past histories of these patients. This writer thought that perhaps proper handling of this condition in childhood might have prevented surgery.

Along this same line it is interesting to review one of the first articles that appeared in the first issue of the ANNALS OF ALLERGY by Dutton.[37] He expressed the idea that the etiology of appendicitis in some instances was due to allergy. He explained that although the first changes were probably of a reversible nature that later they became irreversible with necrosis and vascular change. Microscopic examination of these specimens revealed an allergic type of edema and the eosinophilic infiltration.

There is probably no more interesting, uncertain or hazardous clinical domain in childhood than acute conditions in the abdomen and pain is the presenting symptom, the warning signal, that something has gone wrong and that it may be serious, according to Brennemann.[20] He wrote that the majority of the more serious abdominal conditions heralded and accompanied by pain fall into two main categories: those due to obstruction and those due to infection. He suggested that each of these presents its own characteristic signs and symptoms that vary only with the degree rather than the nature of the underlying condition. He reported that where there was obstruction to any hollow viscus with a muscular propulsive mechanism there was intermittent pain, which may be very slight or very intense depending on the degree and suddenness of the obstruction. If the obstruction was sudden and complete the pain is agonizing, especially at the start, and there may be shock present. This is known as colic no matter what the underlying cause. He emphasized that there was very little tenderness. Pressure, in fact, was often a source of relief and was not infrequently self applied. If the obstruction was partial and gradual in onset, the pain varied with the degree of obstruction. It is always intermittent and it may vary from mild to very severe pain. Hypertrophy, hyperperistalsis and distention, finally atony if too long continued, supervene proximal to the point of closure, and atrophy and contraction distal to it. Brennemann called attention to the fact that in conditions due to infection, the pain is more constant and uniform unless there is a concurrent obstruction. Intermittent periods of greater pain will then manifest themselves. He again emphasizes that tenderness was always present over the affected area and was more pronounced than unelicited pain.

In discussing Brennemann's paper, Peterman[82] commented that many children with recurrent abdominal pain were brought into his office for diagnosis after appendectomy had failed to bring relief. The child with

recurrent abdominal pain demands a careful examination and consideration of the possibility of gastrointestinal allergy and of subacute rheumatic fever. Peterman noticed that these two conditions often explain the obscure pains which may be associated with low fever and slight if any leukocytosis. Allergy causes pain by producing spasm of the intestinal tract and rheumatic fever, by infection. Much of the colic in infants is due to gastrointestinal allergy to foods, particularly when these are introduced too early. He contended that it is a common practice today to introduce new foods long before there is any need for them and long before the infants gastrointestinal tract is prepared for their digestion. Commercial advertising has exerted a pernicious influence of infant feeding in modern practice. He agrees with Brennemann that many of the abdominal pains in children are of unknown etiology but he was of the opinion that these usually disappear under conservative management.

Clein[26] presented some very interesting statistics on the growth and development of 100 allergic children over a period from birth to ten years of age. He called attention to the fact that their first allergic symptoms usually occurred in the first four months of life and were present as a rash or eczema and gastrointestinal symptoms such as vomiting, pylorospasm, colic, excess gas, diarrhea and constipation. According to this observer egg and orange juice were the most common allergens to cause symptoms. Prophylactic and dietary environmental treatment was instituted and was stressed repeatedly at each examination as soon as the patient developed an allergic condition. It was discouraging to learn that although the allergic state was diagnosed in the first few months of life 98 per cent of the infants developed major allergic symptoms during the course of observation. Perennial allergic rhinitis was the most common major allergic symptom occurring in 26 per cent, pollen hay fever in 17 per cent, asthma in 6 per cent, and eczema in 7 per cent. Only one allergic symptom occurred in 56 per cent of the children while the others had multiple symptoms. The essayist has observed that the first allergic symptom in infancy does not usually determine the type of allergy that will develop later. Most of the major allergic conditions develop before six years of age; only 15 per cent in this series occurred after this time. Clein called attention to the fact that although prophylactic treatment in its present state of development will probably minimize or ameliorate the allergy and therefore will allow the child to develop and grow normally yet it does not prevent the development of allergic conditions in the future.

Hill,[90] with his usual conservatism, suggested that with the great increase in the interest in allergy it is inevitable that some should have a tendency to magnify its frequency and importance. He did not censure this tendency for as he says "without a spicing of a few high-powered enthusiasts, allergy would lose much of its flavor." He suggests that it needs a considerable flavoring of conservatism and that all of us who are especially interested in allergy are continually tempted to look for allergy in everything; he warned that we must be careful not to see it where it is not. He commented that it is often said that in bottle-fed infants, colic, chronic vomiting, diarrhea, malnutrition, and pyloric spasm are frequently caused by allergy to cow's milk, and there is not an uncommon tendency to immediately assume the allergic origin of some of these disorders, without taking into account more old fashioned causes. Hill wrote that he would be the last one to deny that some of these disturbances may be caused by allergy. But he called attention to the fact that he firmly believes that they are occasionally so caused, but not commonly. Plain overfeeding, indigest-

ible masses of curded casein, and gas in the bowel have been causes of abdominal distress in infancy for a good many years, according to his observation.

This same author was of the opinion that the older child with recurrent obscure abdominal pain was surely a difficult diagnostic problem. Many of these children were subjected to various tests to rule out infectious and various other conditions of the abdomen. Some of these children who have negative tests have gastrointestinal symptoms due to food but the hospital ward was not a good place to investigate it; if the attacks are at relatively infrequent intervals, it may take months. Occasionally the child or mother knows exactly what food or foods cause symptoms but more often they do not. Hill divided these children broadly into two groups, those with other allergic symptoms such as urticaria or asthma, and those without. In the first group food allergy is usually suspected as a cause of pain and very often it is found. In the second group food allergy is considered a factor but it will not be found as often. The diagnosis of food allergy should not be made until all other causes have been ruled out. He emphasized that it should then be made only upon the most accurately determined evidence. Furthermore, he commented that the relief of symptoms following the removal of a specific food does not necessarily prove food allergy; there may be other qualities about the food in question, entirely apart from allergy, which may cause distress. He commented that this large group of children with recurrent obscure abdominal pain was very interesting and that he was certain specific foods account for some of the cases and that a few of the cases were allergic.

That frequently unrecognized manifestations of food allergy in infancy might be caused by cow's milk or substances eliminated in woman's milk was emphasized by Donnally.[33] As early as 1930 he demonstrated egg white in woman's milk. He also recalled that Matthew Brunner in 1941, showed that cottonseed protein was eliminated in woman's milk as late as twenty-four hours after ingestion. The protein appeared in the milk within a couple of hours after it was eaten. Thus, the principle is established of foreign protein elimination in woman's milk. He commented that, day in and day out, the aggregate amount may be considerable and undoubtedly is enough to cause symptoms. Besides, abdominal pain, vomiting, and diarrhea may be caused and rarely they have found blood in the stools when the infant was sensitive to certain foods ingested by the mother. He also emphasized the fact that common foods which may cause gastrointestinal allergy are cow's milk, eggs, wheat, orange, rice, spinach, string beans and lentils, chocolate, nuts, and fish. This same author was of the opinion that of any of these foods are capable of causing symptoms such as headache and cyclical vomiting which must be differentiated from bouts of acetone body acidosis relieved by ingestion of glucose and fluids.

It is important to note that Wergeland[130] has observed that allergy as well as other conditions may result from human milk. This author has reported three cases in detail, at the Pediatric Department of the State Hospital in Copenhagen, in which human milk had a detrimental effect on the infant. He reported that most pediatric texts listed it as rare, but he suggested that it is important to recognize and start treatment early. This is a report of probable allergy to human milk in the same family which had been treated in the course of three years. Regardless of the type of treatment used all three cases proved to be fatal. It is his impression that probable familial allergy to human milk existed in all three cases. This author is of the opinion that from an etiologic point of view, cases of in-

tolerance to human milk are divided into two groups: (1) intoxication and (2) allergy. The first group comprises cases in which the mother's milk is found to contain substances with directly toxic effect upon the infant in the amount usually employed. It is a characteristic feature of this group that milk is equally harmful to all infants who might drink it. The real factor of importance in this group is a deficiency in vitamin B_1 which occurred while the mother was living on a limited diet during pregnancy and a period of lactation. He continued, that in China where the expectant and lactating mothers often live on a diet almost entirely devoid of vitamin B, this is a disease of some consequence. Formerly it was called "infantile beriberi," but recently it has more correctly been termed "breast-milk intoxication." It appeared that the incomplete oxidation of carbohydrates due to this form of avitaminosis will result in the accumulation of a number of intermediate metabolic products in the tissues, also in the breast milk. A few of these products have a directly toxic effect on the infants according to this author. The result is an intoxication usually of an acute course, and in most cases with a fatal outcome. The second group are definitely due to allergy of breast milk. They may be divided into two groups: (a) allergy to foreign substances in the milk that has been eaten by the mother, and (b) allergy to a human protein contained in the milk. It is important to note that in all three cases the chief symptoms were vomiting and diarrhea. The last two exhibited eczema of the face and scalp. All three were children of the same parents.

Colic, or gastroenterospasm, is the first clinical manifestation of allergy in the newborn of which the parent may complain, according to Glaser.[89] He stated that it usually starts during the first weeks of life and terminates, regardless of therapy, by the time the infant is three months of age. In other words, he suggests that it occurs when the gastrointestinal tract is introduced to foreign proteins, either cow's milk or a variety of others which reach the infant in the mother's breast milk. According to this author, not all colic is of allergic origin, but the severer cases often are, and he suggested that in proportion as the child suffers from colic so may subsequent manifestations of allergy appear in later infancy and childhood. This author states that without going into any further detail, it may be said that the evidence of the allergic origin of colic may be divided into two classes: (1) presumptive and (2) specific. The presumptive evidence is as follows: (a) There is a definite incubation period of ten days to three weeks after birth before colic develops. (b) During the first weeks of life transient positive reactions to cutaneous tests occur which disappear as the child becomes accustomed to the new foods.[34] (c) Transient precipitins also occur in the blood stream to those allergens during the same period.[111] (d) Transient eosinophilia appears as new foods are introduced and disappears as the child becomes accustomed to these foods.[12] (e) Infants who have had colic have eczema more frequently than infants who did not have colic.[131] The specific evidence that colic is due to allergy is its response to changes in diet. For example, the worst colics will often clear up when the formula is modified.

Glaser[89] continued that it was interesting to note the similarity of the incubation period "of colic and anaphylaxis." Something analogous occurs in the child when the foreign protein, milk, is absorbed by the gastrointestinal tract. I refer particularly to cow's milk, as this is the foreign protein most usually encountered by the newborn infant. The process of absorption of cow's milk in the gastrointestinal tract leads to a longer latent period than occurs in experimental animals when a foreign protein

is injected, so that the incubation period of colic is ten days to three weeks. He warned that the pediatrician who is familiar with this phenomenon will, if the child is doing well, not change formula but allow the colic to develop, if it is going to, while a child is on that formula. Then, if necessary, he may make whatever changes that are advisable. The author also called our attention to the fact that colic does occur in the breast fed infant, as well as the bottle fed infant or even in the infant fed exclusively on soybean milk from the day of birth.

However, the failure to demonstrate the etiology of colic in many cases has led to a study of this subject from various points of view. One of the most interesting was that of Pierce who observed the delayed onset of colic in premature infants. He felt that the common type of colic, starting at the age of two or three weeks and terminating spontaneously when the infant is about three months of age, could be most adequately explained by considering that a developmental factor is at least partially responsible for the disturbed physiologic mechanism which causes the symptom complex. He reported the appearance of what seemed to be typical colic in a number of premature infants and observed that its onset was delayed for a period approximately proportional to the degree of prematurity.

Glaser reported that there is a good deal of evidence that pylorospasm and, therefore, presumably hypertrophic pyloric stenosis, are probably on an allergic basis.[29] This condition appears to be the result of long continued pylorospasm and must be due to some allergen which begins to act on the pylorus *in utero*. He was of the opinion that if this was so it was perhaps reasonable to conjecture that other diseases of infancy which may be secondary to spasm of smooth muscle sphincters, as hydroureter and congenital megacolon, may also be on an allergic basis. He suggested that at present the evidence of this is lacking.

That pylorospasm may be due to food allergy was illustrated by a case reported by Balyeat and Pounders.[11] The patient was an infant who was first operated upon because of a diagnosis of pyloric stenosis at the age of four weeks. No evidence of this condition was found at operation. At age three, the symptoms recurred and the child was again operated upon with this same diagnosis and at this operation nothing abnormal was found. He developed eczema while convalescing and by skin testing he reacted to various foods of which egg and milk were proved clinically to be the most important. On elimination of these foods the abdominal symptoms disappeared in twenty-four hours and the eczema within a week.

Hill[90] was of the opinion that there was little doubt that intermittent attacks of vomiting could be caused occasionally by allergy. Yet he did not believe that the common syndrome which we have always called "cyclic" or "recurrent" vomiting has anything to do with food allergy. It was his impression that the appearance of acetone in the urine before vomiting began could be promptly cured by intravenous glucose and insulin, and that the artificial production of the syndrome in susceptible children by a ketogenic diet, all points to this condition as a metabolic disorder.

Kunstadter[63] was impressed at the paucity of articles in the literature regarding chronic diarrhea in infants and childhood resulting from gastrointestinal allergy, although acute disturbances such as pylorospasm, vomiting, colic, and various symptoms simulating organic diseases are frequently mentioned. This investigator concluded that all patients suspected of having celiac disease who do not respond favorably to the "celiac diet" in a reasonable length of time, should be given a diet from which milk has been removed (as well as other possible allergens) before other elaborate

diagnostic procedures are made. He suggested that a careful family history for allergy and a detailed history of the infants' reactions to various additions to the diet should be sought as added evidence. In the event that elimination diet which included milk and possibly other foods does not result in improvement, then further diagnostic procedures can be contemplated, namely, analysis of the fat content of the stools, glucose tolerance, possibly vitamin A absorption, and also enzyme determinations of the duodenal contents. He emphasized that although skin testing may be inconclusive in the diagnosis of food allergy in infants, gastrointestinal allergy should always be considered as etiologic possibility for chronic diarrhea with or without the celiac syndrome, particularly when there is a family history of allergy and when individual foods produce such symptoms as vomiting, abdominal pain, eczema, nasal discharge coughing, et cetera, revealed by careful history. It is interesting to note in the three cases of gastrointestinal allergy presenting the "celiac syndrome" that he reported, evidence was presented in all cases indicating cow's milk as the principal offending food.

McKhann,[71] who reported on five cases with celiac syndrome, commented on the fact that in each of these patients it was possible by skin test to demonstrate some evidence of food allergy, although he noted that this was remarkable because it is well known that skin testing is not a dependable method of determining food allergies, and important food sensitizations may be missed by skin tests and yet be discovered by clinical studies. It was interesting to note that two patients gave strong positive reactions to banana, a food which is often considered an important part of a celiac diet. Elimination of the positive reacting foods was not followed by dramatic response but that there was evidence of a very definite gradual improvement as shown by the improvement in the general condition of the patient and was demonstrable by studies of absorption of glucose and fats from the gastrointestinal tract. In one case there was an immediate and definite increase in the absorption of vitamin A after foods to which the patient was sensitive were removed from the diet.

From these studies, these investigators assume that an association might exist in certain patients between the celiac syndrome and gastrointestinal allergy. Attention was called by these workers to the fact that it is not yet definite whether the allergy is secondary to a disturbance of absorption dependent upon the celiac syndrome or whether the food sensitization precedes and is responsible for the symptomatology of celiac disease. The added observation that absorption from the gastrointestinal tract of a fat-soluble substance, vitamin A, may be impaired in conditions known to be due to allergy but in which gastrointestinal symptomatology is minimal suggests that degrees of impairment of absorption may occur on an allergic basis, and that the gastrointestinal allergy may bear a causal relationship to the celiac syndrome.

Since the symptoms of allergy of the gastrointestinal tract in infants simulates so many other conditions Nance[75] emphasized the importance of making a quick differential diagnosis or at least one that would rule out allergy. The result of his work seemed to indicate that such a method is available in the examination of stools for the presence of eosinophiles. He suggested that many years ago Haughwout[53] called attention to the presence of a large number of eosinophiles in the stools of patients suffering from diarrhea.[74] Lately he decided to look for eosinophiles in the stools of infants showing other symptoms suggestive of gastrointestinal allergy and the results were quite gratifying. In a report he selected ten cases, from

over thirty patients in his practice in the past two years who have shown eosinophilia in the stools, which he considered a representative group found in any pediatric practice. The author is of the impression that the diagnosis of all the cases would have been made eventually without examining the stools for eosinophiles, but in the majority a long period of trial and error was eliminated. He published the technical data necessary in preparing slides to demonstrate eosinophiles in this article and concluded by stating that the examination of mucoid portion of stools for the presence of eosinophiles was of value in recognizing gastrointestinal allergy in infants.

Rosenblum and Rosenblum[95] have followed very much the same line of thought in the investigation of stools for eosinophilia. Sixty infants suffering from diarrhea, vomiting, and colic, either alone or with two or three of these combinations were reported in a series as a study by Rosenblum and Rosenblum. Stool eosinophiles were demonstrated in all cases. They also studied a series of seventy-six infants whose stools were negative for eosinophiles and these included cases of bacillary dysentery, cystic fibrosis of the pancreas, amebic dysentery, diarrhea of undetermined causes, and normal infants having normal stools. In other words, there was nothing in the clinical course of this last group to indicate any evidence of active allergy during the period of observation. The authors emphasized that the presence of gastrointestinal allergy may be suspected when clumps or large numbers of scattered eosinophiles are found in the stools. The outstanding microscopic feature is the abundance of mucus occurring in the stools.

ESOPHAGUS

Allergy of the esophagus may be uncommon when compared to allergic reactions in other sections of the alimentary tract. Rowe[100] fails to list allergy of the esophagus in reporting a detailed analysis of symptoms in one hundred fifty cases of gastrointestinal allergy. Lintz[68] in a series of two hundred twenty-four patients with gastrointestinal allergy observed globus hystericus as one of the general symptoms, but not as an allergic reaction in the esophagus. Jackson[60] has seen erythema and localized edema of the mucous membranes in the esophagus and reported two cases in patients with associated angioneurotic edema and urticaria. The first case, a woman, aged thirty-eight, was seen because of difficulty and pain in swallowing and retrosternal pain extending through to the back. Four days previously she experienced violent abdominal pains, tenesmus, painful swelling of the right hand the upper lip, the lower lid of the right eye and the tip of the tongue. Although the symptoms had improved, they were still present when the patient was admitted. In fact, the swelling of the eyelid afterwards increased and a bleb formed on it and broke. Within a few hours the patient became unable to swallow solids and liquids passed slowly. The process was accompanied by a sense of constriction and a "boring" sensation and pain. There was no history of previous esophageal symptoms but on numerous occasions there had been swelling of the palate and tongue. There was also a history of numerous painful gastrointestinal attacks. During one of these attacks an exploratory laparotomy was performed with negative findings. During two previous attacks, there was painful micturition. The x-ray examination revealed that the thoracic esophagus was close to a small lumen through which the opaque mixture trickled very slowly. The border on edge of the shadow at the constriction was smooth, the operator reported that the esophagoscopic examination showed the

mucosa of the hypopharnyx to be normal but in the mid-thoracic portion, the lumen was almost completely occluded by the firm, swollen, bleeding nodules on the right wall of the esophagus. The ability to swallow gradually improved and at the end of two weeks the second x-ray examination was negative and a second esophagoscopy of the lumen and the mucosa seemed perfectly normal.

The second patient, a woman, aged forty-two was seen because of inability to swallow anything, even water. Difficulty in swallowing solids had appeared suddenly. At the same time urticaria covered both sides of the chest, the back and the left side of the face involving especially the left side of the upper and lower lip and the inside of the left cheek. There was a history of previous attacks, but none had involved the mucosa. Asthmatic attacks seemed to alternate with the urticarial lesions. Dermagraphia was also present, since wheals could be produced by scratching the skin. Roentgen examination showed complete stoppage of the esophagus about six centimeters above the diaphragm. The esophagoscopic examination revealed a normal lumen and mucosa down to about the junction middle with the lower third. At this point the esophagus was completely closed by a firm white nodulous swelling of the walls. Re-examination within a few minutes, using an esophagoscope with a small lumen, revealed an extremely red mucosa with a white ridge, or line, extending down the anterior wall and ending at the constriction of urticaria. About the fourth day the patient reported that she could swallow water without difficulty and the rash had almost completely disappeared. Re-examination showed the esophagus to be normal as to both lumen and mucosa. The second x-ray with opaque mixture also revealed no abnormalities.

Withers[136] reported a case of food allergy of the esophagus in a woman, aged thirty-six, who also suffered with vasomotor rhinitus and seasonal hay fever. The onset was gradual with the complaint of difficulty in swallowing and discomfort at the center of the sternum, but there was no pain. At first the attacks were mild and occurred every three or four weeks but later they became more severe and occurred irregularly at five to seven day intervals. The duration depended upon the severity, lasting from one to four days and then gradually subsiding. All the attacks started with a mild discomfort and then gradually dysphagia and the mucus from the throat would gradually increase in severity for about twenty-four hours. Then it would be impossible to swallow even warm liquids. Pain was then a frequent and distressing factor, located over the lower one-third of the sternum and described by the patient as spasm-like in character and occurring at ten to thirty minute intervals and of ten to fifteen seconds duration and, as she described it, having some of the characteristics of labor pains. The patient's mother, brother and oldest daughter had seasonal hay fever. Roentgen examination during a moderate attack revealed a diffuse irregular outline of the walls of the lower half of the esophagus. Second examination made during a free interval revealed no abnormality. The esophagoscopy during the free interval revealed a normal lumen and mucosa. The patient refused an examination during an attack. The symptoms disappeared under allergic investigation and could be reproduced at will by adding the offending foods which were chocolate, peas and beans. Swineford, Prince and Feinberg all reported in the discussion of this paper esophageal allergy to foods, pollens or physical agents respectively. It is interesting to note the ephedrine sulphate controlled the attacks perfectly. It would have been interesting to know what effect adrenalin or ephedrine would have had on Jackson's patients.

Miller[18] has observed edema of the esophagus in several patients which occurred in less than a minute after the ingestion of a food. The allergic reaction resulted in cardiospasm, dysphagia, discomfort and a feeling of constriction in the esophagus.

STOMACH

Pollard and Stuart[83] observed the gastric mucosal changes in a group of thirteen patients in order to study the effect on the gastric mucosa following the ingestion of a specific food allergen. These observers used the following routine. All patients with gastrointestinal symptoms were repeatedly proved to be sensitive to specific food by deliberate feeding during a previous investigation. Before the controlled observation of the gastric mucosa was made the patients fasted for twelve hours. These investigators then placed a specific antigen in the stomach for thirty to sixty minutes, or until the original symptoms recurred. The stomach was then emptied and a second gastroscopic observation was made.

One patient, studied according to the above program, was a colored woman, aged twenty-two years. Because of a history of repeated episodes of abdominal discomfort and cramps she had been treated by an ulcer diet. This diet not only exaggerated the symptoms but on three occasions she had a severe hemorrhage. Since complete gastrointestinal study had been consistently negative, these investigators suspected egg as being the offending food and subjected the patient to the above mentioned program. The controlled observation of the mucosa showed it to be quite normal. Within fifteen minutes after a soft egg was placed in her stomach she developed the usual upper abdominal cramp-like discomfort. After thirty minutes the stomach was emptied of its contents and the gastroscope was again inserted. These observers noted a striking difference from the first examination. The color of the gastric mucosa, according to their description, was a dull pinkish orange and there was a complete absence of highlights. The mucosa had developed a blotchy, pseudo-polypoid character to it, and the rugal folds had become thickened and almost rigid. Several submucosal bleeding points were observed but no actual bleeding. A thick grey mucus adhered to the mucosa in several areas. They reported that the change just described was scattered throughout the entire gastric mucosa. The symptoms were improved with a hypodermic of adrenaline; unfortunately, after the removal of the gastroscope. The patient was completely relieved of her symptoms by eliminating egg from her diet.

Four patients who were being treated for bronchial asthma due to food, but who did not have gastrointestinal symptoms, showed on gastroscopic examination a uniformly different appearing mucous membrane. There was a mild hyperemia and increase in the number of highlights with a glistening appearance to the mucosa but there was no nodulation or edema present. One patient with asthma not due to food and with no gastrointestinal symptoms and two controlled cases with no family or personal history or allergy were tested in the same manner with egg and salmon as specific allergens and no degree of hyperemia or edema occurred as was seen in the patients with the gastric disturbances following the ingestion of the specific allergens. In other words, the control patients showed a gastric mucous membrane of only moderate hyperemia and mild bogginess of the mucosa but in no way comparable to the patients who were clinically sensitive to specific foods.

These investigators suggested that the characteristic changes that are typical of allergy were as follows: a distinct hyperemia, lumpy or even

nodular appearance, edema and thickening of the rugal folds with diminished peristalsis, and greyish mucus clinging to the mucosa. These changes involve mainly the lower one-third of the stomach. Sub-mucosal hemorrhage were seen in one patient. They further stated that from these observations they believe that it is possible to produce alterations in the stomach mucosa which result in clinical symptoms from the ingestion of a specific allergen and that with repeated insults the changes in the stomach mucosa may become irreversible and result in permanent damage. They warned that in cases of indigestion where the etiology is not clear, allergy to a specific food as a possible explanation should be considered.

This report of their observations is extremely interesting and very valuable. They have not only demonstrated, but they have seen gastrointestinal allergy due to food.

A few years later Lichstein and Benjamin[66] reported a case of transient allergy edema of the stomach, which was observed during an asthmatic attack. Their patient, a white man, aged forty-eight, was first seen in the hospital in February, 1947, for headaches and epigastric pain. There was a history of asthma and skin rashes of many years duration. Two operations on the sinuses gave no relief. An appendectomy had been performed seven years previously. Epigastric pain of four weeks duration was associated with nausea and vomiting and some degree of dizziness. The patient volunteered the information that he was very nervous. Roentgenograms made in April reported a definite distortion of the stomach in the pre-pyloric region consistent with pyloric ulcer with associated spasm. X-ray pictures made elsewhere previously were said to have disclosed the presence of an ulcer.

In May 1947 the gastroscope was again used. It passed easily but the angulus was not readily seen because of mucus. When a clear view was obtained a well circumscribed rather superficial ulcer was seen on the lesser curvature of the angulus. It was reported to be about one centimeter in diameter with a reddish boarder but there was no infiltration. The remainder of the body and cardia were easily visible and apparently normal. The impression of the operator was that there was a benign peptic ulcer of the anterior wall at the lesser curvature present.

A second gastroscopy in June 1947, revealed a normal gastric mucosa. The ulcer formerly observed was not seen. Towards the end of this examination the patient developed asthma and a rather sudden change developed in the stomach while the gastroscope was still in place. The folds of the lumen of the lower portion of the body became markedly swollen and there was such an increase in secretion as to obscure the greater curvature and the anterior and posterior walls of the stomach. Discomfort and retching of the patient excluded further observation. The stomach, as observed through the gastroscope, was normal at first but this was soon followed by an unusual swelling of the mucosa during an attack of asthma.

In August 1947, the patient complained that the nausea and vomiting had returned after an interval of a few weeks while he was on ulcer therapy management. A neuropsychiatric impression was that he was suffering from an anxiety neurosis with a possible histaminic cephalgia. In September he suffered with urticaria which appeared over the face, body, and scrotum and did not disappear after the use of adrenaline. The gastric symptoms were improved at this time.

The third gastroscopy was a planned experiment and was performed in September 1947. The patient was prepared in the usual manner, special precautions taken not to cause undue excitement. A severe attack of

asthma occurred much earlier than was anticipated but the patient cooperated well. The observer reported as follows: "The angulus was immediately seen and during the ensuing five minutes the stomach folds became increasingly reddened and increasing amounts of mucus were secreted. The mucus was thin in consistency and numerous bubbles formed. The folds were then seen to become thicker and edematous. Some swelling was visible in the antrum, but this was not as marked as in the body. One-half cc of 1:1000 adrenalin was given subcutaneously and a profound change occurred in two minutes. The swelling decreased markedly, the color of the mucosa varied to a pale orange red, and the secretion diminished to a point where we were visualizing a dry stomach."

In their discussion Lichstein and Benjamin felt that it is important to emphasize that in the majority of the cases reported the involvement of the gastric reactions seemed confined to the antrum. These investigators felt that it was significant that in their case they visualized the edema in the body of the stomach. They also commented that in the light of the quoted considerations it would appear that the superficial ulcer they described in the first gastroscopy may have had an allergic basis. They were of the opinion that in the future it would seem wise for the gastroscopist to consider allergic edema or allergic gastritis as well as other forms of gastritis when he encounters bogginess, hyperemia, and hypersecretion of mucus. They contend that the gastroscopic impression would be confirmed if, at repeated and prolonged intervals, examinations showed a sudden disappearance of the pathologic findings.

This reviewer felt also that this was an interesting and direct observation that was made on the gastric mucosa of an asthmatic. Whether such prompt action of adrenalin would reduce a more severe edema in the intestines as promptly as it did in this case is problematical. In the discussion of their case, these authors included some interesting reports of other investigators in the field. Since the original articles are in French, and also are not readily available, this reviewer takes the liberty of reporting them very much as they were written.

Chevallier,[25] in 1935, was probably the first to report gastroscopic appearance of edema of allergic origin. He observed the transient gastric edema due to bee venom in a beekeeper who, following bee stings, developed attacks of fainting, urticaria and, twelve hours later, epigastric symptoms simulating pyloric stenosis. At this point gastroscopy revealed transient edema of the antrum which disappeared as clinical improvement occurred.

Pavoit and Chevallier,[81] in 1936, discussed, among many cases, one case in which transient edema limited to the antrum and musculus sphincter antri was seen through the gastroscope. This reaction occurred in the stomach of a young girl who repeatedly had experienced violent gastric cramps from milk or eggs four hours after their ingestion. Simultaneously, there was vomiting, itching and angioneurotic edema of the skin, and headaches.

These same authors emphasized the importance of considering transient edema of the stomach as a possible differential diagnosis by roentgen-ray in deformities of the pre-pyloric area. They cited thirty-six cases of this entity with strikingly impressive roentgen-ray studies in which various types, such as the generalized massive type, a massive type involving the lesser curvature the pseudo-ulcer type, those with total edema of the sphincter antri, the group with partial edema, erosions of the lesser curvature and "fleeting hemorrhages" were classified. In some it appears that,

roentgenologically at least, edema of allergy closely simulated carcinoma of the stomach.

There has been some evidence presented indicating that even more profound and chronic changes in the stomach may be present as a result of an allergic reaction. Chevallier and Moutier,[23] in discussing the stomach and skin diseases, reported gastroscopic findings in eight cases of chronic urticaria and five of angioneurotic edema. They reported diffuse atrophic gastritis in nine patients; four were normal.

Chevallier and Moutier[22] in 1946 observed eleven cases of angioneurotic edema of the stomach. In five, there was massive edema but the visceral edema did not invariably coincide with surface edema. It was also noted that changes of the gastric mucosa occurred from one examination to another. Afendoulis in 1948 reported three cases of "allergic gastritis," in which the signs were those characterizing chronic "inflammatory" gastritis and emphasized the immediate manifestations of symptoms and the intensity of the process.

As Schindler[105] suggested in his book and also as noted by Pollard and Stuart,[84] that with repeated gastric intestinal allergic insults, two things may happen: first, acute transient edema, which may cause the stomach mucosa to eventually become irreversible and result in permanent damage; second, chronic atrophic gastritis, one of the causes of indigestion.

Many symptoms referable to the stomach may be allergic in origin. If the symptoms are acute and occur soon after the ingestion of a food or a drug, differential diagnosis may be easy, as demonstrated by the cases just cited. However, if the symptoms are those of chronic indigestion and the symptoms are delayed long after eating, then the diagnosis of allergy may be more difficult to establish, regardless of whether or not there is a family or personal history of associated hypersensitive conditions.

Indigestion is one of the commonest complaints for which patients consult physicians.[67] It consists of varying degrees of epigastric distress, sense of fullness and distention in the epigastrium, nausea, heartburn, cramps, and intestinal distention with the passage of flatus. This symptom complex can occur as a result of a great variety of conditions and the exact symptoms give no clue as to the underlying cause.

The commonest underlying causes of indigestion include: (1) organic disease of the stomach, gastritis, peptic ulcer; (2) diseases of other abdominal viscera, such as chronic cholecystitis or appendicitis; (3) diseases of the heart, such as coronary sclerosis or congestive failure, and (4) the most common cause is stimuli of nervous origin.

However, regardless of the etiology, the symptoms, as in allergy, are due to a disturbance of gastrointestinal motility involving, in varying degrees, spasms of portions of the tract and flattening or partial reversal of the normal gradient from the pharynx to anus.

Since allergy can mimic both an organic or functional disease, considerable investigation may be necessary to establish the hypersensitive reaction as a cause of indigestion.

The etiology of peptic ulcer is still unknown.[91] That ulcers develop as a result of localized necrosis is generally accepted but the causative factors, which bring about this necrosis, have been subject to much controversy and speculation.

The most important role as causative factors in the development of peptic ulcer are now considered to be disturbances of enzyme balance (such as pepsin), disturbances of hormonal influences (such as enterogastrone), hyperacidity, hypermotility fatigue, psychic trauma or stress, excessive

use of alcohol or tobacco, dietary excesses or imbalance, focal infection, gastric or duodenal endartery thrombosis or spasm, excess vagal activity and allergy. It was suggested that none of these possible etiologic factors have been entirely discarded, although pepsin imbalance, body type, allergy and focal infection, are receiving little prominence in current medical literature.

In a study of gastrointestinal allergy, with special reference to peptic ulcer, Ehrenfeld et al,[38] concluded that there was no valid reason to assume that allergy plays an important part as an etiologic factor in peptic ulcer.

In a series of seventy-five patients with proved peptic ulcer, eight, or about ten per cent, were found to have allergic conditions. This was about the usual incidence for allergy in the general population.[49] Four, or 55.5 per cent of the seventy-two, definitely allergic patients, had peptic ulcer. Again, this was well within the incidence of peptic ulcer in the general population, according to Rehfuss.[92] It is of interest to note, however, that according to these investigators, nineteen of the seventy-two allergic patients presented symptoms which mimicked the ulcer syndrome. Repeated x-ray examination of the stomach and duodenum, a transient spastic phenomena without a demonstrable niche was present in eight patients. It was the opinion of these investigators that this may explain the occurrence of a clinical entity, the symptoms of which closely resemble those of peptic ulcer.

They reported that of seventy-two allergic subjects, eight suffered with urticaria or angioneurotic edema. In four, or half of this group, spastic findings in the stomach or duodenum could be demonstrated by x-ray. They felt that this fact lends support to the explanation of Demel[31] that gastrointestinal allergy is due to angioneurotic edema of the mucous membrane and that the localized spasm demonstrated by x-ray may be associated with, or due to, the presence of this edema or wheal.

It is generally believed that allergy does not produce a demonstrable reaction in the gastric mucosa. However, there are those who believe that peptic ulcer may result from food allergy. Kern and Stewart[62] stated that they were convinced that there is strong evidence that duodenal ulcer is occasionally due to food allergy and, furthermore, in some cases it may be one of several associated or complicating factors.

These investigators made detailed observations on food allergy on thirty-two unselected adult ulcer patients. There was operative proof in twenty patients and in the other twelve, x-ray and the clinical history was used as evidence. In this series they reported a personal history of allergy in 40 per cent and a family history of allergic conditions in 25 per cent, which they signify as high above the figures of incidence for the general population. Although these investigators observed in detail the results from skin tests and clinical feeding in the whole group, yet they were specially interested in that group of six cases with a recurrence of ulcer after operation. In four of the six, diagnosis of a recurrent ulcer was based on the history, and on x-ray findings, and in the other two the ulcer was found at operation. There was a personal or family history of allergy in four of the six patients, and in two patients both were present. Only one of this group could eat food which gave a positive skin reaction without ill effects. These investigators were of the opinion that evidence as presented tends to indicate that food allergy may be an etiologic factor in a small but appreciable percentage of cases of duodenal ulcer. They emphasize that this is especially likely in those in which there was a recurrence of ulcers after a previous operation.

Bockus[16] suspected that allergy may be a factor in producing symptoms in some patients with peptic ulcer but he doubts that it is a primary or fundamental cause. Since his statements are of great interest, the reviewer would like to quote verbatim from a chapter entitled "Etiology and Pathology of Gastric and Duodenal Ulcer" under the heading, "Allergy and Peptic Ulcer":

"The experiments of Gray and Walzer are of fundamental importance in establishing a possible mechanism for abdominal symptoms in allergy, but there are other links to be added before the chain of evidence establishing allergy as a cause of peptic ulcer is complete. Many allergic persons seem to possess the autonomic nervous system imbalance which is charactertistic of many ulcer-bearing people, namely vagus preponderance. Peptic ulcer occurs in patients with other allergic diseases and a family history of allergy is not uncommon among ulcer patients. Sensitivity to foods may be found in association with peptic ulcer and it is difficult at times to relieve the ulcer symptoms until the foods responsible are eliminated from the diet. Other peculiarities in the clinical behavior of peptic ulcer suggest the possibility of an allergic factor. No one has satisfactorily explained the tendency toward ulcer recurrences in the spring and fall of the year. Furthermore, the beneficial effect of foreign proteins injected parenterally has been ascribed by some observers to a desensitization phenomenon. Some massive ulcer hemorrhages have been thought to arise from increased capillary permeability, possibly on an allergic basis. Rarely, acute complete pyloric obstruction may develop almost overnight in an allergic person known to have a peptic ulcer, and the symptoms and signs of obstruction may disappear abruptly, when the diet is restricted to a single food to which the patient does not react. These observations suggested that allergy influences the behavior of certain peptic ulcers, but no absolute proof exists for assigning to allergy a primary role in the formation of chronic peptic ulcer. Nevertheless, in the management of ulcer patients allergy always must be considered. The co-existence of food allergy and peptic ulcer constitutes a formidable team, troublesome to manage and perhaps increasing the probability of occurrence of hemorrhage and obstruction."

For years it has been the custom to prohibit tobacco as part of the treatment of peptic ulcer. This rationale has been purely empiric. It may be recalled that Harkavy[52] showed many years ago that the general run of ulcer patients were sensitive to tobacco in a distinctively higher percentage than the general run or normal individual.

This reviewer has just recently observed a physician with seasonal hay fever, asthma and a definite history of peptic ulcer. While he was in the Navy seven roentgenological examinations were made at various times and locations over a period of four years; all were negative. Complete relief of the ulcer-like symptoms followed the elimination of milk, chocolate and fresh pork.

That the pylorus plays an important part in the allergic symptomatology of the stomach is becoming increasingly apparent, according to Fries.[42] He suggested that any survey of several factors underlying pyloric obstruction must include hypersensitiveness. In this study he selected thirty children ranging in age from four to fourteen years, who had repeatedly exhibited marked gastrointestinal disturbances within a few minutes after the ingestion of small amounts of allergenic foods. There were positive intracutaneous reactions to the offending foods in many of the children. In the control study plain barium sulfate in water was used. On roentgenologic study made about a week later barium sulfate in water plus the

offending allergen was added without the knowledge of the patient. A predetermined amount of allergen required to produce a definite gastrointestinal disturbance varied from 2 to 12 cc (½ to 3 drams). This amount was insufficient to alter the normal roentgenogram in normal subjects.

Both series were subjected to intermittent fluoroscopy within the first thirty minutes. In the control series the barium began to leave the stomach immediately or within ten minutes which is considered normal. In the allergen series it required twenty minutes or longer for the allergen-barium meal to pass from the stomach to the duodenum in twenty of the twenty-eight children studied. This investigator suggested that the roentgenograms in most part confirmed the fluoroscopic findings. He observed that one patient, who was sensitive to three different foods (eggs, fish and nuts), responded with the same gastrointestinal symptoms on different occasions. After a trial feeding with each of the offenders involvement of the pylorus was demonstrated by x-ray in each case. This author suggested that his study seemed to support the findings of others who, by gastroscopic examination of the stomach during an allergic reaction, observed that the involvements seemed primarily to involve the pyloric region. He was of the impression, based on his own studies, that an allergic reaction in the region of the pylorus might account for the epigastric distress, the cramp-like nature of the pains and the rapid onset of symptoms followed ingestion. It was his suggestion that the spontaneous relief which occurred was due to the elimination of the antigen either by vomiting or passage to the lower bowel and suggested a contact reaction. He felt that this was further substantiated by previous studies involving the rectal installation of the antigen where he observed that contact provoked an immediate onset of symptoms which were accompanied by spasm as observed roentgenologically in the large intestine. He concluded that the gastric retention in this report and in his previous studies may be attributable mainly to blockage of the pylorus. He observed the roentgenograms revealed transient abnormalities whose configurations sometimes resemble those of fixed organic lesions. He emphasized that reexposure to the same allergens resulted in reactivation of the same shock tissues and that exposure to other antigenic foods produced the same symptoms in the same patient, and they also produced similar responses in the pylorus.

SMALL INTESTINE

There is probably less known of the allergic reaction in the small bowel than other sections of the alimentary tract. A number of papers have appeared in which there has been an attempt to show a more or less characteristic x-ray pattern of allergic reactions in this section.

In a study of twelve cases of gastrointestinal allergy, Tallant, and his co-workers,[118] endeavored to establish clearly the value of the x-ray as an aid in the diagnosis of food allergy in the small bowel. At first a control test was made by studying the reaction of the small intestines with a barium water mixture. This test was made at least five days previous to feeding the offending allergen and the results were considered normal. Four days later the x-ray studies were repeated, using a test meal of barium and the suspected allergen. There was a definite motility change in the small bowel in all of the patients.

One patient reported for a third study using egg to which he was not clinically sensitive, and the motility of the small intestine was again found

to be normal. Eight nonallergic persons were observed in a similar fashion, using egg, milk, pork and corn, all with negative findings. These investigators then studied five allergic patients in whom food produced allergic reactions other than intestinal disturbances. Although their allergic conditions (asthma, angioneurotic edema and neurodermatitis) were precipitated by the food tests, no changes were noted in the motility of the small bowel. It would appear from these demonstrations that the value of the x-ray in the examination of the small bowel in the study of food allergy is definitely established and possibly answers some of the past criticisms.

Schloss[110] reviewed the numerous investigative procedures used for establishing the etiologic diagnosis of intestinal allergy and adds a new type of investigation. He suggested the use of a balloon-tipped, double lumen intestinal tube by means of which numerous phenomena may be studied by the kymographic recordings. In his opinion it was possible to observe the degree of tonicity and rate of motility in a selected segment of the intestine, and the changes in these functions occasioned by the oral or tubal introduction of suspected food allergens. By this method he hopes to determine the reaction interval and the duration of reaction as well as the effect of the therapeutic agents, all to be evaluated *in vivo*. By means of the Miller-Abbott balloon technique this author was able to confirm the production of the motility disturbances by introducing the predetermined allergens directly into the jejunum. Motility changes in the small intestine had previously been revealed by x-ray studies after the feeding of the suspected allergen. Schloss emphasized that the intubation procedure was not recommended for routine use for the discovery of allergenic foods. He suggested routine gastrointestinal studies and x-rays in order to exclude observable organic lesions. Further clinical observation, and elimination diets are useful as a screening process for the implications of specific foods. Next, he suggested that roentgenologic study with barium mixed with the suspected foods and, finally, the use of the intubation procedure may be employed to substantiate the diagnosis. Schloss was of the impression that the method just described provides an additional means for the investigation of allergy of the intestinal tract. It would appear that Schloss' experiment would add further support for the usefulness of the x-ray technique of a small bowel examination of food allergy.

Lepore, Collins and Sherman,[65] in an excellent article, endeavored to evaluate the usefulness of a small intestine x-ray examination as an objective technique in twenty patients with suspected gastrointestinal allergy. The method, as described by these investigators, was according to the technique of Golden[47] using four ounces of barium sulphate in normal saline solution. The motility was observed fluoroscopically and films were made at appropriate intervals. The especially stressed features were: (1) gastric emptying, (2) transit time of barium from the stomach to the cecum, (3) mucosal pattern, (4) tonicity (caliber of the lumen of the intestine), and (5) segmentation or lack of continuity of the barium column. Most of the patients selected for investigation gave histories suggesting food allergy with gastrointestinal disturbances. The alimentary symptoms consisted of flatulence abdominal pain, and often diarrhea and nausea following the ingestion of specific foods. Urticaria followed the ingestion of the offending food in half of the patients, and several exhibited marked eosinophilia but, as a rule, the eosinophil count was not elevated. They explained that the commonest allergen was whole milk, which oc-

curred in 70 per cent of the cases. These observers reported that the results of their studies showed two patients who were strongly suspected of food allergy but showed no significant change in the motor function of the small bowel. Motility changes that were observed in eighteen of the twenty, however, consisted of the following: (1) hypermotility with rapid transit of barium from the stomach to the cecum in fourteen patients (hypomotility was encountered in four patients), (2) hypertonicity of the small intestine, especially the middle and lower portions, and (3) segmentation or discontinuity of the barium column. At times gastric emptying was delayed, but this was not a constant finding.

It was interesting to note that these observers could provoke by clinical means, by administration of the specific allergen during the x-ray study, symptoms of abdominal stress, cramps and diarrhea. Elimination of an offending allergen resulted in a significant and often dramatic clearing of symptoms. These investigators suggested that antihistaminic drugs, such as elixir of Benadryl, Pyribenzamine, Neoantergan, and Perazil, were helpful in relieving acute symptoms and also in the treatment of patients whose multiple sensitivities precluded the use of an elimination diet for any period of time. They suggested that it was possible when antihistaminic medications were given, small amounts of food allergens could be permitted in the diet.

Of considerable interest to allergists was the observation that many patients exhibited motility changes in the small intestine before the allergen was administered at the time of examination. These changes, they emphasized, when present were accentuated by feeding of the offending allergen. These investigators stated that in the past it has been assumed that most changes might represent the carry-over from previously ingested food allergens. They explained that another theory is that the motility changes in the small intestine may result from an intrinsic or constitutional state of irritability of the small intestine (probably related to acetylcholine liberation) rendering the small bowel of these patients peculiarly susceptible to the stimulus of various cholinergic trigger mechanisms, such as, histamine, chemical, bacterial, mechanical irritants, or psychogenic disturbances. Further study is being made of this important point and includes the investigation of anticholinergic drugs, such as Banthine. These authors are of the opinion that the role of food allergy in the causation or aggravation of organic disease of the intestine, stressed by many and deprecated by others, has lagged because of the lack of objective methods of study. By the use of the x-ray method of examination, using the method explained above, they feel that it has been possible to produce marked disturbances of motility in food sensitive patients, thus verifying the clinical histories of food sensitivity.

In the chapter on allergy in his monograph, *Radiological Examination of the Small Intestine,* Golden[47] concludes that, thus far, the evidence seems to indicate that a small intestine study of a food sensitive patient in the absence of the allergen may show: (1) nothing abnormal, (2) an abnormally rapid transit time through the small intestine, usually with hypertonicity of the middle and lower tubes; or (3) hypertonicity with a slower than normal transit time. He wrote that it was of interest that the upper part of the small intestine seemed to show nothing abnormal. When a patient ingested a food to which he was specifically sensitive, the small intestine study was as follows: (1) often showed slow emptying from the stomach; (2) may show nothing definitely abnormal in the small intestine; (3) may disclose a slow transit time with the segmentation

indistinguishable from the appearance seen in milk deficiency states; or (4) infrequently may show a rapid transit time.

This author emphasized that a diagnosis of intestinal allergy cannot be made on the basis of the roentgen examination at the present time. He suggested that if hypertonicity of the lower half or third of the small intestine appears, particularly when associated with a slower transit time, it seems proper to suggest the possibility of food allergy as a working basis which should be investigated further. This author stated that he has seen a number of cases in which this suggestion has been followed by the elimination of offending food with relief of the symptoms.

Some obscure factors in the production of unusual small bowel patterns was recorded by Goin.[46] He was of the opinion that the effects of the various emotions on the intestinal tract was extraordinarily well known. He was surprised to learn that in spite of this widespread and common knowledge that we, as physicians, gave such little thought to the emotions and emotional conflicts as a possible factor in producing a great deal of the abnormal gastrointestinal behavior. Vomiting due to pyloric obstruction and pain and vomiting from intestinal obstruction usually offer no great problem of diagnosis to the roentgenologist. In general, he claimed it is their part to establish, or to eliminate the possibility of organic disease. Nevertheless, he admitted there were times when it was possible to suspect emotional disturbances or an unconscious conflict if it is kept in mind that these reactions are not infrequent and that they lead to disturbance of the gastrointestinal tract.

Following these remarks he presented a case of profound emotional conflict which was actually diagnosed from x-rays of the gastrointestinal tract. A white woman, fifty-four years old—and it is essential to her history to state that she was Jewish—complained of vomiting, abdominal pain and diarrhea for twenty-two years. During that time she had undergone fifteen operations with no relief from her symptoms. The patient did not appear acutely ill, had lost no weight, and except for heavy scarring of the abdominal wall, the physical examination was negative.

Shortly after admission to the hospital, an allergen-free opaque medium of barium sulfate in normal saline solution revealed a normal pattern and behavior of the intestinal tract. During the examination the patient talked freely with the examiner and told him that she was allergic to pork—but no one would listen to her or believe it.

With this in mind the possibility occurred to Goin that this educated and cultured individual who believed herself agnostic, was suffering from an unconscious conflict; that when she ate pork it resulted in an emotional storm which passed over the sympathetic chain and produced a marked and dramatic effect in the gastrointestinal tract.

The patient was advised that it would be necessary to repeat the gastrointestinal study. Finely ground pork was mixed with the barium, normal saline solution and she was unaware of any difference between this mixture and the one used during the first examination. The roentgenologic examination was negative; identical to the first one that was made on admission. The fact that she had taken a great deal of pork with no changes in the behavior of the gastrointestinal tract was thought to eliminate pork as an allergen. She was very co-operative and willing to submit to the third examination. The same opaque medium was used as in the other examinations and soon after it had been taken she ate a small piece of well cooked pork. Within thirty minutes she experienced violent abdominal pain and an x-ray film of the abdomen showed a striking

change in the small intestine. Goin suggested that this was an objective demonstration of a psychic lesion—an emotional storm resulting from an unrecognized conflict in the unconscious. In conclusion this author made it plain that the roentgenologists have become increasingly conscious of the small intestine and its diseases. As a matter of routine they recognized cicatrizing enteritis, ileocecal tuberculosis, tumors and manifestations of dietary deficiency. But in this instance he explained the purpose of his paper was to direct attention to other causes for alterations in the behavior of the intestinal tract and that these causes may be as far apart as the psychological states and specific allergies.

A case of gastrointestinal allergy simulating regional enteritis was reported by Blumstein and Johnson.[15] They reported that their patient, a man aged twenty-six, had experienced three similar attacks of abdominal distress and tenderness in the right lower quadrant. The first occurred March 13, 1949, and lasted twenty-four hours. The second on April 27, was more severe and lasted forty-eight hours. The third attack occurred on June 5, and lasted one day.

The history showed that during the next attack he was admitted to the hospital, on July 6, 1949, because of mid-abdominal cramping pain of eight hours duration, associated with nausea but no vomiting. The morning after admission the tenderness and milk rigidity in the right lower quadrant was still present and rebound tenderness was now evident. The white blood cell count had risen from 13,400 to 16,000 and the eosinophiles had risen from 2 to 7 per cent within twenty-four hours. Temperature was still normal and the urine was normal. Three previous attacks and the present one was thought to be due to acute appendicitis.

Operation was performed under spinal anesthesia. There was about 50 cc of clear fluid in the abdominal cavity and the appendix appeared to be normal. About 35 cm of the terminal ilium was markedly thickened and edematous.

Because of the three previous attacks it was reasoned that there was a persistent regional enteritis and that immediate resection was justifiable. The possibility of it being an allergic reaction of the small intestine was not considered. About 45 cm of the terminal ilium was resected, along with the right part of the colon, and ileo-transverse colostomy was performed. The specimen of the resected ilium was thick and edematous. The vessels of the serosal surface were congested and there was a white mottling under the serosal surface. The surgical pathologist's report on the histologic sections was as follows:

"Sections of the terminal ilium show a marked edema of the submucosa and subserosa. The entire wall is infiltrated by myriads of eosinophilic leukocytes. The process is apparently an entirely allergic one, without any evidence of ulceration of the mucosa or of an ordinary pyogenic infection. Lymph nodes in the mesentery show dilatation of the sinusoids with edema and eosinophilic leukocytic infiltration. These changes suggest very strongly that this is an allergic enteritis."

The patient made an uneventful recovery and returned to work after a short convalescence. During the next four months he experienced three attacks of abdominal distress, all following the ingestion of sea food. The second attack was quite severe and lasted twenty-four hours. It did not respond to the usual therapeutic doses of ephedrine, epinephrine and antihistaminics. The patient has remained well since avoiding sea food, after the third attack.

These authors felt that this patient fulfills all the necessary requirements for the diagnosis of gastrointestinal allergy. He had a personal and family history of allergy, and the relationship between the ingestion of sea food and the attacks of abdominal pain appears to be established beyond any reasonable doubt. Finally, the microscopic appearance of the resected ilium showed a typical picture of an allergic response.

The symptoms of acute gastrointestinal allergy of the small intestine are often uncomfortable but the reactions are usually transitory and there is complete recovery. Occasionally the attacks are more severe and simulate an acute abdominal attack and are sometimes operated upon because of a mistaken diagnosis, as the case just described. The following is a report of a fatal case of irreversible allergy of the entire small bowel.

According to Berne[18] a fifty-three-vear-old Italian man was given an intramuscular injection of penicillin on three different occasions. Following the second injection of penicillin, the rash on the arms and legs became much worse and the following day bullae formed over the entire body and puffiness of the face had developed. Ephedrine and Pyribenzamine were very effective and caused a rapid clearing of the skin. Following the third injection of penicillin, which was given for a low grade pneumonia, a generalized exfoliative dermatitis, most marked on the hands and feet, and generalized urticarial eruptions, swelling of the face, eyelids, hands and feet with severe pitting edema of the lower legs was observed. Purpuric rash covered over half of the body. Further treatment was ineffective and the patient expired.

At necropsy the walls of the duodenum and the remainder of the small intestine and cecum were very friable and there were diffuse hemorrhagic areas of necrosis in the mucosa. The hemorrhagic mucosa of the jejunum and ileum showed marked superficial ulcerations. The stomach and colon were normal except for the hemorrhagic lesions of the cecum. This author observed that the lesions were chiefly limited to the skin and the small intestine. He also called attention to the fact that in the more advanced lesions both the arteries and veins, as well as the surrounding tissue, showed necrosis with cellular reaction.

Rowe,[104] in 1953, reported three patients with supposed infectious regional enteritis which were due to food allergy. The first a woman, aged forty-one, who complained of abdominal pain, cramping and diarrhea was rapidly relieved of her discomfort and continued free of it for five years on a milk free diet. The skin tests and the leukopenic index were negative to milk. The diagnosis was established by the history and the x-ray findings and later confirmed by microscopic examination of a surgically removed portion of the inflamed ileum.

The next patient, a woman aged thirty, experienced symptoms of regional enteritis from the ingestion of milk, eggs and fruit. The symptoms could be reproduced at will by clinical testing. A change in physicians permitted a change in the diet. Shortly after using a soft general diet the abdominal symptoms gradually increased until finally there was obstruction of the terminal ileum which resulted in resection of this portion of the bowel. For two postoperative months, the patient experienced four to six loose stools daily while using a soft diet. The authors are of the opinion that the operation would have been avoided if the elimination diet had been maintained.

The third patient, a woman aged forty-nine, remained practically well for sixteen months on a fruit free diet consisting of rice, tapioca, white potato, lamb, pureed carrots, squash, sugar, salt and water. Cortisone given

orally in doses of 25 mgs three times daily for nine days hastened the recovery. These authors emphasized that the evidence accumulated by Andresen and Rowe over a period of years that food allergy is a major cause of chronic ulcerative colitis necessitates a closer study of the role of allergy in regional enteritis. They explained that the localization, spreading tendency, remissions and recurrences, fever, occasional inherited predisposition, and the relief obtained with x-ray therapy and Cortisone can all be explained from the standpoint of allergy.

GALL BLADDER AND APPENDIX

Walzer and his associates,[129] in 1943, produced allergic reactions in the gall bladder of the rhesus monkey. This edematous reaction was transitory and closely resembled those they produced previously by passively sensitizing the mucous membrane of the ileum, colon and rectum in man. According to these authors food allergy has been known to cause pain in the upper right quadrant for many years. They suggested that in the differential diagnosis of pain in this region of the abdomen that allergy of the gall bladder and biliary tract should be taken into consideration especially when the patient is an allergic individual. They wrote that many investigators have observed that the clinical symptoms produced by food allergy may simulate those of cholecystitis and cholelithiasis. These symptoms included gaseous distention, nausea, vomiting, dull or colicky pain in the right upper quadrant, tenderness over the gall-bladder region associated with tenderness of the trapezius muscle. The possibility of allergy should always be considered in patients who complain of gall-bladder symptoms with negative x-ray findings. Exploratory operations have revealed normal gall bladders. In many instances where relief was not obtained by surgery the elimination of certain foods from the diet has given relief, as noted by many observers.

Rowe[102] wrote in his monograph on food allergy many years ago that hepatic and biliary allergy probably account for many of the symptoms which do not respond to medical and surgical treatment.

It may be well to remember that all pain in the upper right quadrant simulating gall-bladder disease is not necessarily due to allergy in the gall bladder. The discomfort may result from allergic spasm of the colon in the region of the gall bladder as was demonstrated by Eyerman.[39]

Graham, Cole and their colleagues[48] wrote in their monograph on diseases of the gall bladder and bile ducts that the conditions which are likely to have been mistaken for chronic cholecystitis are numerous. One which is frequently confused with gall-bladder disease is that of intestinal allergy. They emphasized that the possibility of confusion caused by intestinal allergy has received almost no mention but that the importance of considering it in the differential diagnosis is great because the symptoms can imitate very accurately those recurrent attacks of cholecystitis. In their opinion, patients who are subject to respiratory allergy should receive special attention in order to exclude intestinal allergy if there is any doubt of the diagnosis of cholecystitis. The authors reported two cases that have brought this matter to their attention very forcibly. The first case, the surgeon was surprised to find a normal gall bladder, but nevertheless he established drainage. A few days after the patient had returned home his former symptoms recurred. Further investigation revealed that he was a hay fever and asthma sufferer and that also he was sensitive to wheat, the ingestion of which produced typical gall-bladder symptoms. The second patient who was under the medical management of

Eyermann, was also sensitive to wheat. The cholecystographic examination was normal and it was found that she could reproduce her attacks at will by the ingestion of wheat.

The reviewer[137] takes this opportunity to report the following case: A housewife, aged thirty-eight, was referred for the treatment of nasal allergy of ten years' duration. There was also a history of indigestion, bloating and pain in the upper right quadrant for the past two years. Before the studies for the treatment of nasal allergy were completed the patient experienced so much abdominal discomfort that the gall bladder which contained stones was removed. She was assured that the operation would relieve the abdominal distress and also probably "take care" of the nasal condition as it might be a condition secondary to the gall-bladder disease. For the next five weeks it appeared that the gall-bladder operation had ended all of her sufferings. But shortly thereafter, she noticed a slight rhinorrhea one morning and a few days later it was accompanied by nasal stuffiness. Two weeks later all the gastrointestinal symptoms experienced previously had recurred. A continuation of the allergic studies revealed that the nasal symptoms were due to inhalants and milk and that the gall-bladder symptoms could be reproduced at will by repeated feedings of milk, potato and pork.

New viewpoints in the pathogenesis and therapy of chronic cholecystitis were presented by Szilard, Rauss and Szabo.[117] There were seventy patients with gall-bladder complaints in this series. It was found that coli bacillus occurred most frequently in the secretion of the duodenum. It was their contention that the blood of patients with chronic cholecystitis contained agglutinins against homologous coli strains found in the duodenal secretions. It was observed that all agglutinations occurred with homologous strains, and no agglutinations were noted in the non-allergic controlled patients. These investigators contended that the duodenal juices contained pus resulting from allergic inflammation rather than from coli infection. Upon administering small doses of prepared vaccine, unusual local and focal reactions did occur which tend to support their theory. A vaccine prepared from non-agglutination, but homologous coli strains produced local toxic infiltration but did not produce any focal reaction. These investigators are of the opinion that a new light is thrown on the characteristics of chronic cholecystitis in that it is a disease of focal origin.

Abdominal pain in the right lower quadrant may be allergic in origin. Edema and constriction or spasm which occurs in the colon may simulate appendicitis, while a chronic irreversible allergic reaction in the appendix may result in appendicitis.

Dutton[37] has observed appendices which on histological examination revealed the edema and eosinophilic infiltration of an allergic reaction. In reviewing the history of a number of patients before and after operation, he reported that there was often a discrepancy between the clinical and the subjective findings as compared with the pathological findings in the histological picture. This observer is of the opinion that the involvement of the cecum or other portions of the intestine in the allergic reaction may explain the failure of many patients to be relieved of symptoms at operation. He differentiates the conditions simulating appendicitis from one in which there is an irreversible allergic reaction that occurs in the appendix, leading to appendicitis. He emphasized that in this instance the treatment is surgical.

Sneirson and Mazar,[114] in 1951, reported that they operated on a patient

with acute abdominal symptoms suggesting appendicitis. At operation there was a good deal of clear fluid in the abdominal cavity and a bright red bowel which was well demarcated distally and diffuse proximally. They suggested that the mesentary was block shaped with no similarity to the "v-shape" seen in mesenteric thrombosis. Tendency towards hemorrhage called their attention to the possibility of allergy. Postoperatively they obtained a history of acute "bellyaches" which always accompanied eating green peppers. They also learned that even small amounts of milk acted as a very definite laxative in this patient. They concluded that in cases which come to surgery the failure to recognize the allergic entity may result in further needless surgical procedures.

COLON

Andresen,[9] in 1941, was so impressed by the wide divergence of opinion regarding the etiology and treatment of ulcerated colitis that he wonders whether the various writers were discussing the same entity. He explained that some would write with great conviction about infection due to bacteria while others, discarding the bacterial idea, attempted to show that virus was a causative factor. Each writer stressed the specific treatment for infection but, actually, we found that symptomatic treatment was depended upon for the relief of symptoms. He explained that non-specific therapy, artificial pyrexia, had been used with some success, adsorbents and sedatives have always been prescribed, and a careful diet was usually insisted upon. He noted that the diets that were found to be the most successful were those that had eliminated milk completely from the diet.

Andresen emphasized the fact that in 1933, he called attention to the importance of allergy as a cause of this disease and also called attention to its successful treatment on that basis. And yet although other methods of treatment have been tried and found wanting little attention has been paid to the allergy theory.

In discussing the role of allergy in the etiology of this disease it is well to consider whether the theory of allergy would conform to what has been accepted as criteria of this condition. The author explains that the pathological lesions of ulcerated colitis have been quite definitely described and may occur in a part or in the whole colon at one time. In the early stages hyperemia, hypersecretion and mucosal edema are present and punctate rash, resembling herpes, are usually seen. He continued to explain that as a result of localized ischemia, areas of necrosis develop and slough out, leaving ulcerated areas, and when they coalesce, often cause extensive areas of denudation of the mucosa, with small islands or tabs of mucosa still visible. These denudated areas may bleed upon the slightest trauma or tearing of the small vessels may cause more severe bleeding. Deep sloughing may produce single or multiple perforations, with resulting local or general peritonitis and later adhesions, deformities, kinks or obstructions. Induration he explained, with infiltration by leukocytes, often found to be eosinophiles, may disappear with healing or may result in fibrosis, with marked narrowing or stiffening of the colon. The mucosal lesions may disappear entirely, or with long continued irritation, may result in polypoid changes, in which carcinoma may, but does not often, develop.

This observer emphasized that the microscopic changes in the sensitized mucosa of hemorrhoids and colostomies and the microscopic changes in the sections of sensitized intestinal mucosa of the rhesus monkey which occurred during an allergic reaction as shown by a series of experiments

by Gray, Walzer, Harten, et al[50,127,129] were practically the same as those described in the early stages of ulcerative colitis. Andresen commented that it did not require a great stretch of the imagination to realize that repeated or continuous reactions of this type would result in the more serious lesions seen in the severe cases of this disease.

The symptoms may be readily explained on the basis of the pathological findings. The author was of the opinion that the irritation set up by the allergic reactions in the mucosa caused spasms and general hypermotility with resulting diarrhea and tenesmus. The number of stools may vary from one to twenty or thirty per day. The bleeding, sloughing and ulceration produce the typical stools or rectal discharges, containing blood, mucus, shreds of mucosa, and, when infection was present, also some pus. Anorexia or actual disgust for food, resulting in insufficient digestion and incomplete absorption by the damage of the intestinal mucosa over which the contents are hurriedly propelled, often result in emaciation and dehydration, with evidence of multiple food deficiencies. Complication, of course, will usually add to the gravity of the situation.

Regardless of whether or not specific organisms have been found and thought to be playing an important part in the etiology and the prolongation of this disease it was important to conduct a study to determine whether allergy was the primary or contributing factor. Andresen was of the opinion that skin tests are not sufficient and he abandoned them altogether. He found by clinical means that food allergy was a principal cause of ulcerative colitis in thirty-three of fifty patients or a total of 66 per cent. He found that the elimination of milk, the offending food in 84 per cent of the cases, and all milk products from the diet frequently resulted in dramatic symptomatic improvement. He was of the opinion that if foods were the cause of the disease the responsible food must be consumed regularly and in fairly large amounts over a long period of time in order to produce lesions severe enough to cause ulcerative colitis.

Andresen concluded by stating that food allergy may be primary or a complicating factor in ulcerative colitis and that the symptoms are easily explained on the basis of this condition. He insisted that the proctoscopic and roentgenologic examination should be used to demonstrate the clinical effects of allergenic foods as they are tested. He contended that the treatment based on allergic management has produced better results than those based entirely on an infective etiology.

Bockus[17] stated that he or his co-workers have rarely observed such rapid changes in the sigmoidoscopic appearance of the mucous membrane as reported by Andresen following the withdrawal of suspected food allergens in cases of acute, active ulcerative colitis. Sigmoidoscopic examinations have been made on patients both after the feeding of a suspected allergenic food and after the suspected foods have been eliminated for days when only intravenous therapy was used.

This author contended that although this type of study was only done occasionally a continuation of such observations is indicated in light of the experimental work of Gray, Walzer, et al. He suggested that it would be interesting to note the effect of local applications of the suspected or proved allergenic substance.

Although a detailed allergic history was taken and diet observations were made on all patients with gastrointestinal complaints, there was no evidence that food allergy occurs any more frequently in patients in early stages of ulcerative colitis than in those with other gastrointestinal conditions. Bockus suspected therefore, that the specificity of allergy in the

pathogenesis of most cases was doubtful. However, it appeared that it was his contention that a state of hypersensitivity may be induced by tissue reactions secondary to the disease process, and therefore he did not discredit the importance of allergy as a factor in the continuation and severity of this disease.

In an article on chronic ulcerative colitis Rowe[96] summarized his observations of twelve years of the study and treatment of this condition. The erythematous, eczematous-like, inflammatory lesions which are seen in this condition are often due to food or drug allergy but may result from pollen or other inhalants. He contended that when allergy was the only cause, the symptoms and tissue changes gradually improved with the control of the allergies. When there were complicating factors, however, such as infection, anemia, hypoproteinemia or avitaminosis, it was as important to control these as it was the allergies in order to obtain good results. He stated that severe ulcerative colitis can be due to allergic reactions to foods, drugs or inhalants with or without the above secondary complications. Rowe felt that allergy best explained the primary lesions of this disease. The erythema, edema, and easily bleeding mucosa may be due to vascular allergy as in atopic dermatitis. He further compared the lesions in these two locations by the fact that the clinical characteristics, course, and response to proper allergic treatment of cases of atopic dermatitis due to ingestion and/or inhalant allergens should also occur if these same factors were responsible for similar lesions in chronic ulcerative colitis.

The herpetic ulcers which arise from the minute vascular thromboses and result in oral canker sores may also occur in the colon as a result of food, drug or bacterial allergies. With low resistance secondary infection may take place and cause fever, fistulae, abscesses, perforation and peritonitis.

The remissions which occur in chronic ulcerative colitis, he said may be explained by the tendency to refractoriness to causative allergens, such as observed in clinical allergy, explaining recurrent asthma, allergic headaches, or angioneurotic edema. The seasonal variation of symptoms may be due to pollen allergy or the variation of symptoms as observed in food allergy.

He contended that the tendency for allergy to localize in specific tissues and to limited area of one tissue and the tendency of atopic dermatitis can explain the localization and spreading characteristics of chronic ulcerative colitis.

While he believed that the fever was usually due to the complicating infection of ulcerative colitis, it may be due to allergy, especially to foods or drugs.

In the treatment of this condition Rowe emphasized that the allergic reaction of foods, drugs and inhalants should always be taken into account. In the milk cases, his fruit-free elimination diet and later the minimal elimination diet usually controlled the food allergies. In the more severe cases, however, he suggested the strained meat-liquid formula. If nausea and severe anorexia were present intubation of this feeding may be necessary. If inhalant allergies were suspected hypodermic administration of extracts of these factors, along with strict environmental controls, was in order.

Rowe warns that adequate and experienced treatment based on probable allergy was the treatment of choice. When "early ileostomies" are done before such treatment is given fair trial, the operation is not justified, regardless of the low mortality rate that results with the antibiotics and present surgery.

It was his contention that surgery should be reserved for those cases where perforation and peritonitis threaten life in spite of the vigorous use of sulfa and antibiotic drugs, or in cases of uncontrolled perianal infection or of abdominal abscesses or intestinal infection continuing in spite of the present therapy.

Another article on allergy of the gastrointestinal tract was written by Andresen[6] in 1951. He suggested that after the various reports which have appeared in medical literature during the past few years it hardly seemed necessary to discuss the proof of allergic reactions in the gastrointestinal tract. He wrote that the researches of Walzer and Gray,[50,129,127] Rowe,[99,103,101] and Vaughan[126] have shown the specificity of reactions as well as their rapidity of occurrence after ingestion of allergens and the duration as well as the effects of therapy. He contended that after all it was a daily experience of clinicians and patients alike to discover that the ingestion of certain foods invariably cause such symptoms as heartburn, nausea, distention, cramps, diarrhea, migraine, as well as such directly observable lesions as canker sores in the oral cavity and ulcerative colitis in the rectum and sigmoid. Andresen emphasized that there was one outstanding feature of ordinary allergic reactions and that was their rapid disappearance upon the withdrawal of the offending factor. This may be observed in urticaria of the skin and as well as in the uncomplicated ulcerative colitis lesions as soon through the proctoscope.

In the gastrointestinal tract the allergic reaction may be a localized area or occur throughout the tract. Acute gastroenteritis may occur and the reaction will continue as long as the offending allergen is being taken or remains in the tract. Usually they are more or less localized in the mouth, esophagus, stomach, gall bladder or appendix. Milk irritations in the small intestines may produce pains and diarrhea but the more chronic changes may result in the typical findings of regional enteritis. The colon is frequently affected. Milk allergic reactions, he pointed out, may be accompanied by peristaltic unrest, mild tenesmus, or diarrhea, often alternating with periods of constipation, and mucus may be seen with formed or loose stools. This syndrome is known as mucous colitis, irritable or unstable colon. Chronic allergic irritation, he related, may result in changes in the bowel wall starting with redness and edema and continuing through the stages of area ischemia, sloughing, hemorrhage, perforations, adhesions and obstructions, producing the condition known as idiopathic ulcerative colitis or colitis gravis.[8,9,10,97]

Andresen insisted that the diagnosis of gastrointestinal allergy was not simple, but it appears that few allergists or internists seemed to want to give the time necessary for such a detailed study. The variation and severity of the symptoms naturally cause some difficulty in diagnosis. Since they may resemble those of true organic disease, it is always necessary before considering the diagnosis of allergy to rule out any possibility of organic disease by a complete gastrointestinal study and, if indicated by the symptoms, complete study of other symptoms. He emphasized that history of known reactions following the ingestion of certain foods may be of value. For example, the patient who reports heartburn after eating oranges or chocolate or one who has nausea or vomiting after eggs or migraine after whisky, or the patient who says the milk always causes diarrhea, should all be suspected of allergy. The x-ray examination not only determines the presence of organic lesion but may show certain changes in gastrointestinal function and form, that may be quite characteristic of allergy. He suggested that endoscopy of the esophagus, stomach

and rectosigmoid will not only help in ruling out organic disease but may demonstrate the redness, edema, infiltration and ulceration associated with allergic conditions. He remarked that a physiological test is of value, especially in some sudden acute reaction suggesting an "acute abdomen." In this instance a hypodermic injection or even sublingual administration of epinephrine, ephedrine or one of the newer antihistaminic drugs, may give such prompt and complete relief of symptoms as to suggest allergy.

The laboratory examinations should not only rule out organic disease but strengthen the diagnosis of allergy. This investigator insisted that the finding of the specific allergic factor was the real problem in any allergic condition and he contends that determining the specific foods clinically is sometimes an arduous task. Diet study, in his experience, is the most reliable method of determining the specific food sensitivity. For many years he has employed two simple test diets each consisting of only five or six foods which he has designated as test diets No. 1 and No. 2. In his hands they have proved to be very satisfactory. These diets may be found in various articles by this author or in certain text books.

In the final discussion of this paper, Andresen had this to say:

"In closing, I wish only to discuss one subject, that of ulcerative colitis. I am constantly seeing patients who previously have been subjected to all of the known treatments for ulcerative colitis, including typhoid vaccine, intravenously, immunization to specific organisms, psychotherapy, and thorough antibiotic therapy, and they still have ulcerative colitis. Then on diet alone, without any medication, these patients promptly begin to get well. Following up these patients over the years, we find exacerbations if they eat the foods to which they were allergic or new ones to which they have become allergic, but otherwise they remain well for years, with even gradual disappearance of polypoid lesions. If that is not proof of an allergic etiology I do not know what would be considered proof."

In discussing the medical management of chronic ulcerative colitis, Mackie[72] reports that satisfactory allergic studies were completed in sixty-seven cases. Classification was based on the subjective phenomena reported by the patient and also on the appearance of the mucous membrane of the rectum and the rectosigmoid after repeated proctoscopic examination after each change in diet. The clinical evidence of active food allergy was obtained in forty-four cases. In seven others the evidence was equivocal. He reported that history of allergic disease in the patient or in the patient's family was not a common finding, and that idiosyncrasies to various foods had been reported by about half of the cases. In order of frequency the most common foods to cause symptoms were milk, egg, orange, wheat, spinach, and tomato. Mackie suggested that these observations have led him to certain conclusions concerning the mechanism of chronic ulcerative colitis which he stated as follows:

"The phenomena of the disease appear to result from the combined action of a number of factors. There is infection, probably always mixed in character, of the affected portion of the wall of the colon. Both the secretory and the motor physiology of the gastrointestinal tract are adversely and variously affected.

Sensitization of the colon to foreign protein of bacterial and dietary origin plays an important role in the mechanism of relapse and activity of the disease. Not infrequently secondary deficiency states occur and assume major clinical importance."

While the recognition of food allergy was of considerable importance in patients with uncomplicated gastrointestinal disturbances, it was of even greater significance in the patient without organic gastrointestinal disease to which it may be a contributing factor, suggested Lepore, Collins and Sherman.[65] They illustrated their point by presenting a case with nonspecific ulcerative colitis. C.K., a thirty-two-year-old merchant seaman, developed diarrhea and abdominal cramps in October, 1948, for which he was treated in the hospital for two months, and the diarrhea subsided. In May, 1949, he had a recurrence of bloody diarrhea during which time he lost thirty-five pounds. He was living in a hotel room at that time and subsisting on a diet chiefly of milk, despite the fact that he knew that milk had caused diarrhea in the past. Sigmoidoscopy on July 5, 1949, revealed severe and classical ulcerative colitis. X-ray study of the small intestine revealed hypermotility, segmentation, and hypertonicity which was present before but markedly accentuated after taking milk. The laboratory studies were negative except for 32 per cent eosinophilia. Twenty-four hours after he stopped taking milk and used Neo-Antergan, 50 mg before each meal and at bedtime the diarrhea lessened, and within seventy-two hours he was having semiformed stools. Improvement was dramatic and he gained weight quickly. His clinical improvement was accompanied by sigmoidoscopic improvement and within one month he was in a complete clinical remission.

The patient was seen occasionally and in March, 1950, he reported that after feeling perfectly well and gaining thirty pounds that he had developed a recurrence of bloody diarrhea almost immediately after a violent family quarrel which had occurred three weeks previously. He had lost thirty-six pounds during the three weeks in spite of the elimination of milk and the use of Neo-Antergan. The sigmoidoscopic findings were typically those of acute severe nonspecific ulcerative colitis. The eosinophilia was 19 per cent. The treatment this time consisted of Banthine, an anticholinergic drug which has a selective action on the gastrointestinal tract. A dramatic remission was induced within twenty-four to forty-eight hours and this was well sustained so that within five weeks he had regained almost ten pounds and was having one formed bowel movement daily without blood or mucus. The eosinophile count dropped gradually from 19 to 1 per cent for the fourth week of treatment.

These investigators commented on this case as follows:

> "For some years Andresen[9] has suggested that food allergy is responsible to a large degree for the illness called ulcerative colitis. The case just described could support this belief. However, in our experience, the striking sequence of events just listed has been the exception rather than the rule. It is of interest that in this patient the initial episode of colitis treated by us responded dramatically to an elimination diet and an antihistamine. The second episode appeared to have been initiated by an emotional upset rather than an allergic stimulus and, curiously enough, this attack was also accompanied by a high eosinophile count. Apparently, a psychogenic cholinergic stimulus has reproduced the picture which one year before had been initiated by milk allergy. The beneficial effect of Banthine, an anticholinergic drug, was so striking that further investigation of this phenomenon has been initiated and will be the subject of a later report."

In a report of gastrointestinal disturbances attributed to allergy, Squier[115] stated that Andresen[10] believed that recurring attacks of gastrointestinal allergy becomes continuous and are of major importance in the

etiology of chronic ulcerative colitis. Squier suggested that in a series of one thousand allergic patients, they found only two who had chronic ulcerative colitis and in neither of these was allergy considered of etiologic significance nor were sensitivities to foods discovered. Nevertheless, he commented, Andresen's observations extending over several years indicate the importance of a careful and unprejudiced search in such patients for evidences of gastrointestinal allergy.

RECTUM

Allergic reactions occurring in the rectum are of the same nature as those occurring in other sections of the alimentary tract. Thomas and Renshaw[113] reported on characteristic reactions in the form of edema, erythema and vascular congestion observed proctoscopically, and appearing after the application of certain allergenic substances to the rectal mucosa in patients who were suffering from intestinal allergy. Following the positive mucosal action, the patient usually experienced abdominal cramps and rectal discomfort.

Miller[19] explained that in the rectum and around the anus, pain, tenesmus and discomfort can be caused by edema of allergic origin. He rightly suggested that pruritus ani is a symptom that commonly has an allergic basis, frequently not due to the absorption of foods to which the patient is sensitive but to contact agents that produce eczematoid, edematous, and pruritic areas. He has observed that in many instances the causative factor has been some contacted substance, such as wool, rayon, silk or dyes or other substances of clothing, cosmetics, or local medications. He emphasized that it is very important to eliminate other factors in the rectum and around the anus before a diagnosis of allergy is made.

Pruritus ani, or itching of the anal and perineal region, is a common and troublesome complaint.[67] There are many possible etiologic factors. They may be grouped as infectious, allergic, mechanical, and nervous-emotional.

The patient may be sensitive, not only to local or distant bacteria or fungi, but also to foods, drugs (including laxatives) taken systemically, remedial agents (including resorcinol, metals, and local anesthetics) applied locally for relief of itching or for hemorrhoids and the sulfite in cheap toilet tissue. If allergy is suspected as a causative factor an antihistaminic drug may be used as a therapeutic test. If it gives relief, allergy may be strongly suspected as a possible etiologic factor. This reviewer has seen a number of patients with pruritus ani but seldom has food as an allergen been proved to cause the discomfort. However, it does occur.

MISCELLANEOUS

Ingelfinger, Lowell and Franklin[57] in a critical review of the diagnosis of gastrointestinal allergy suggested that it was frequently entertained. occasionally evaluated but rarely established. Allergy, at one time or another has been ascribed to a great number of gastrointestinal complaints, especially those of obscure origin, such as peptic ulcer and ulcerative colitis. To summarize all the articles supporting allergy as an etiologic possibility would be confusing and, further, they contended that most articles on the subject were insufficient to prove or disprove the causative role assigned to allergy. There are three measures used to demonstrate gastrointestinal allergy according to these investigators: experimental studies, clinical observations and laboratory tests.

They contended that various experimental procedures did not provide

conclusive evidence for the spontaneous occurrence of allergic reactions in the human gastrointestinal tract, but they did indicate that the animal or human gut might be the site of allergic reactions resulting in recognizable changes of function.

The diagnosis of gastrointestinal allergy by clinical means is dependent principally on the patient's incrimination of specific foods. They felt that after a careful analysis of these criteria, they were found to be quite unsatisfactory. The reliability of trial diets, theoretically the best of these diagnostic methods, is impaired by the expectations and attitudes of the patient, as well as by the possible error in their execution and interpretation, but most of all by the vague nature of gastrointestinal allergy itself. The laboratory tests may be especially misleading according to these investigators. The radiologic study, they contended, has many pitfalls which they usually summed up by the question: "How can we be sure that the changes that were induced were allergic rather than nonspecific?" They reported that skin tests, as well as the leukopenic index, enjoyed a varied reputation in the diagnosis of gastrointestinal allergy. Before the significance of the eosinophiles in rectal discharges or mucus could be properly evaluated, they recommended that examination of rectal material was necessary in various other intestinal disorders, since a necrotic neoplasm or the ulcerative process of colitis might produce eosinophiles as a result of tissue destruction.

In summary, Ingelfinger and his associates believed that to prove that a patient's gastrointestinal symptoms were due to allergy it would be necessary for the symptoms to result by contact with a specific substance that was innocuous to most of the population; an immune mechanism should be evident in their pathogenesis, and the lesions or functional changes in the gastrointestinal tract should be demonstrable.

A study of the use of soybean milk as an aid in prophylaxis of allergic disease in children was made by Johnstone and Glaser.[61]

The purpose of the study was to determine whether the incidence of atopic dermatitis (eczema), gastrointestinal conditions, and other major allergies, as well as their allergic sequelae in potentially allergic infants, may be influenced by competely withholding cow's milk from their diets from birth to the age of six to nine months.

Ninety-one infants either offspring or siblings of one or more individuals with one or more major allergies, made up this experimental group. They were kept on a diet completely free from cow's milk. According to these investigators, the allergic histories of this experimental group were comparable to those of sixty-five siblings and 175 unrelated control children. It was found that major allergic disease developed in 14 per cent of the experimental group fed soybean milk, while 64 per cent of the siblings and 52 per cent of the unrelated group developed symptoms while using cow's milk. Atopic dermatitis and other allergic conditions often resulting from cow's milk occurred approximately four times more often in the two control groups. Allergic sequelae to allergy to cow's milk occurred in 16 per cent of the experimental group as against 75 per cent of the siblings and 60 per cent of the unrelated group.

These investigators reported that their data suggested that the complete withholding of the first food commonly ingested by potentially allergic newborn infants (cow's milk) for a period of six to nine months might offer a hope of decreasing or minimizing the incidence of the most troublesome allergic disorders in young children.

In an editorial concerning soybean as a milk substitute for potentially

allergic infants, Hill[56] stated that it is common sense not to expose a potentially allergic child unnecessarily to well known allergens, yet they are usually exposed to many such allergens to which they do not develop a sensitivity.

The article by Johnstone and Glaser,[61] Hill contended was founded upon logical premises, and goes farther than previous attempts at the prophylaxis of allergic disease, since they have observed their patients over a longer period of time. Their claim, that withholding cow's milk from a potentially allergic infant during the first few months not only prevented sensitization to other allergens, such as pollen, animal danders, and dust in later childhood, he suggested, is an extraordinary one. He doubted that it would find ready acceptance. He commented that the feeding of a newly born infant on soybean food is hazardous and has the possibility of doing more harm than good. Hill suspected that there is some unknown substance in soybean flour which often causes mild to severe diarrhea, which most pediatricians would not risk unless it was proved a necessity by existing evidence of milk allergy. Hill felt that, although milk is a common allergen in the infant's diet, it is presently being overemphasized. It was his contention that milk-free infant foods have a definite and valuable place in treatment but that they are used too often in situations which have nothing to do with milk allergy.

For an excellent discussion of gastrointestinal allergy the reviewer would recommend that the chapter by Miller[19] in *"Gastro-Enterology"* should be read. Miller commented that every competent physician now realizes the important part played by allergy in the production of the digestive tract symptoms and suggested that, obviously, the gastrointestinal internist must be "allergy minded."

Piness,[85] whose work is familiar to all allergists, has just written one of the best chapters on the subject. It is very concise and compact, and yet he re-evaluates the scope of and the advances in the field of gastrointestinal allergy in a very interesting and complete manner. It is recommended to anyone interested in the diseases of the alimentary tract, regardless of the cause.

Probably one of the most practical reviews of the subject of gastrointestinal allergy was written by Kohn.[28] It contains many useful and interesting remarks. This article has been previously reviewed in these pages and, therefore, will not be repeated here. For the readers of this review who are interested in the practical aspects of this subject, it is highly recommended.

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1418 Bryant Bldg.

In Memoriam

LEWIS PALAY

We regret to announce the death of Dr. Lewis Palay, who has been a Fellow of the College since 1945. Doctor Palay lived in Miami Beach, Florida, and practiced medicine for twenty-two years. Since 1942 he had limited his practice to allergy. He graduated from the Central High School, Cleveland, Ohio, in 1919, and from Western Reserve University in 1924. He received a Ph.G. degree in 1923 and A.B. degree in 1924, from Adelbert College. He was a graduate of the University of Louisville Medical School in 1928, and interned at the Bronx Hospital from 1928 to 1930. He took postgraduate studies at Polyclinic Hospital Medical School, where he also had postgraduate training in allergy.

Doctor Palay was a member of the American Medical Association, the Dade County (Florida) Medical Society, and a charter member of the Florida Allergy Society (Section of the Florida Medical Association) of which he was elected secretary shortly before his death. He was a Fellow of the American Academy of Allergy, member of Alpha Omega Alpha honorary society, a diplomate of the National Board of Medical Examiners, and a diplomate of the American Board of Otolaryngology. He was on the staff of Mt. Sinai and Jackson Memorial Hospitals, and was attending allergist for the National Children's Cardiac Home in Miami. He had been a member of the Bronx Hospital and Lincoln Hospital in New York, and served on the United States Selective Service System Board in Bronx, New York. He was a member of the Bronx Hospital Clinical Society and served as its president from 1941 to 1942. He made important contributions to the subject of allergy, particularly in the field of surveys of pollens and molds.

Doctor Palay is survived by his wife, Tedi, and two young daughters, Marcia and Roberta.

Doctor Palay was known for his genial pleasant manner and ever willing cooperation which endeared him to his colleagues. He was a member of the College whom the officers respected, and they join the members in extending sincere sympathy to his family.

EDWARD GEORGE TATGE

Edward George Tatge, a Fellow of the College since its inception, died suddenly September 7, 1953, at the age of fifty-three. Doctor Tatge was born in Chicago, Illinois, and graduated from Englewood High School in 1917. He received a B.S. degree from Northwestern University in 1921, and his M.D. degree in 1925. He interned at Evanston Hospital. Doctor Tatge held teaching positions at Northwestern Medical School and in the Department of Medicine of the Evanston Hospital from 1928 to 1940. From 1940 until the time of his death, he taught at the University of Illinois Medical School and was a staff member of St. Francis Hospital in Evanston. He was a member of the Chicago Medical Society, the Chicago Society of Allergy, Illinois State Medical Society, The Association of Allergists for Mycological Investigations, Inc., Pi Kappa Epsilon, Honorary Medical Fraternity, and other medical societies.

Doctor Tatge limited his practice to allergy. He was one of the earliest members of the mold association and was one of the stalwarts on whom the group could depend for practically any type of investigative work. In many of these investigations, he went out of his way to devote sufficient time, which he really did not have, to

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Letters to the Editor

NATIONAL SOCIETY FOR MEDICAL RESEARCH

I note your News Item in the March-April issue of the ANNALS OF ALLERGY concerning statements by Doctor Robert Gesell of the Animal Welfare Institute. This Institute is apparently proposing an elaborate plan of government regulation of the details of animal experimentation, particularly in medical research, and has made serious charges unsupported by evidence reflecting on the moral integrity of biological scientists.

These articles of criticism on animal experimentation are furnishing material which the antivivisectionists use. The National Society for Medical Research is attempting to give the public factual knowledge about the methods, results and benefits from animal experimentation and is promoting sound public pound laws to protect pet owners and at the same time provide for the use in scientific research of unclaimed impounded animals which would otherwise be uselessly destroyed. This the AWI opposes and the National Society for Medical Research repudiates completely any insinuation that it is not at least as concerned about humaneness as are any self-professed "Welfare" or "Humane" groups. In fact, the National Society for Medical Research is constantly promoting better conditions for animal care, and trying to promote scientific discovery for the benefit of man and animals—which the AWI is impeding by devious methods.

MAURICE B. VISSCHER, Ph.D., M.D.,
Vice President, National Society for Medical Research

ACCIDENTAL OVERDOSE OF CHLOR-TRIMETON WITH NO SEVERE LASTING EFFECTS

An accidental overdose of Chlor-Trimeton has demonstrated that this antihistamine may possess unusual safety. The procedure is, of course, not recommended for determining the safety of a drug but as a result of the following incident it is good to know that serious sequelae probably are unlikely following an overdose.

Examination of a twenty-five-year-old white woman, complaining of rhinorrhea and lacrimation of one day's duration, showed a typical acute rhinitis with reddened edematous nasal mucosae and conjunctivitis. The patient's wedding was planned for three days hence, so she was desirous of a "quick cure."

Chlor-Trimeton Maleate Injection, 100 mg/cc, was injected intramuscularly in this patient. Through error, the dose given was 2 cc (200 mg). The patient left the office but returned in a few minutes because of vertigo, numbness, a tingling sensation over her entire body, and extreme drowsiness. The pulse rate was 120 per minute and blood pressure 90/60. The patient appeared pale and seemed drowsy. She received immediately 25 mg Dexedrine sulfate orally. This dose was repeated in one-half hour. Approximately three hours elapsed before the patient felt sufficiently awake to leave the office. The numbness and tingling sensations had disappeared. The patient stated that her "cold" was gone and no rhinorrhea or lacrimation was apparent. The following day, she was symptom free and had no aftereffects. Her sister came into the office that day with a similar condition and requested the same medication. Chlor-Trimeton Injection was given to her also but this time, of course, in the correct therapeutic dose of 10 mg.

Errors in dose of medication such as occurred here are regrettable but it was

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News Items

THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

This national allergy society held its annual meeting at the Palmer House, Chicago, October 15 and 16, 1953, with cocktails and dinner Thursday evening, and the following program beginning at 9:15 a.m., Friday morning:

President Kenneth L. Craft, M.D.—"Introductory Remarks"
Joseph L. Goldman, M.D.—"Bacteriologic and Cytologic Criteria in Nasal and Sinus Disease"
French K. Hansel, M.D.—"Allergic and Other Untoward Reactions to Antibiotics and Drugs"
William H. Evans, M.D.—"The Use of a Suspension of Cortogen Acetate with Chlor-Trimeton Maleate in the Treatment of Allergic Rhinitis of Pollen Origin"

Case Reports

Leland H. Prewitt, M.D.—"Psychogenic Allergy"
C. W. Armstrong, M.D.—"A New Diagnostic Aid in Allergic Deafness"
G. L. Loomis, M.D.—"Vasodilator Therapy for Nerve Type Deafness"
Sam H. Sanders, M.D.—"Sinusitis—Allergy Plus Surgical Treatment"

Ocular Allergy Symposium

Albert N. Lemoine, Sr., M.D.—"Common Manifestations of Allergy in Ophthalmology"
Phillips Thygeson, M.D.—"Observations of Non-Tuberculous Phlyctenular Keratitis"
S. Albert Hanser, M.D.—"Use of Cortone and Chlor-Trimeton Solution in the Treatment of Allergic Conjunctivitis"
Irving Henry Leopold, M.D.—"Therapeutics of Ocular Allergy."

The Society is also planning to hold a two-day interim meeting next June primarily for the presentation of instructional courses, panel discussions, study classes, et cetera, for the benefit of the membership. Preliminary announcement of this meeting is carried in the April-May-June Bulletin of the Hansel Foundation.

ACADEMY OF PSYCHOSOMATIC MEDICINE

On May 31, 1953, at the Plaza Hotel in New York City, a new society named The Academy of Psychosomatic Medicine was founded. The specific object of its incorporation is to be the advancement of the scientific knowledge and practice of those aspects of medicine which relate to the interaction of mind, body and environment, by means of study, laboratory and clinical research, meetings, and discussions in co-operation with other workers in these and related fields.

Membership will consist of Charter Fellows, namely, those who enrolled at the previous meeting held one year ago, and Founding Fellows (those who join before the first of January, 1954). The Constitution allows for Honorary and Emeritus Fellows.

The requirements for membership as Fellow can be obtained from the Secretary, Ethan Allan Brown, M.D., 75 Bay State Road, Boston, Massachusetts.

The other officers elected at the Founding meeting included Dr. William Kaufman, of Bridgeport, Connecticut, as *President,* Dr. B. B. Raginsky, of Montreal, Canada, as *Vice President,* and Dr. Alfred J. Cantor, of Flushing, New York, as *Treasurer.*

The first scientific meeting will be held in New York City in June, 1954.

Details concerning the new Society may be obtained from the Secretary, or the other officers.

THE AMERICAN COLLEGE OF ALLERGISTS

Decennial Instructional Course and Decennial Congress
Roney Plaza Hotel, Miami Beach, Florida

April 5-10, 1954

The *Decennial Instructional Course,* April 5-7, 1954, with Dr. Ethan Allan Brown, Chairman, and Dr. Hal Davison, Co-chairman, will have forty instructors. Arrangements have not been completed. The following outline, therefore, is tentative and subject to change. See the November-December number of ANNALS OF ALLERGY for further important announcements regarding the program, and the January-February number for the complete program.

Monday morning, April 5, there will be eight lectures on THE ALLERGIC NOSE. Dr. Hans Selye will be guest speaker at the luncheon, and his subject will be "Stress and the Allergic Disorders." Seven lectures on THE ALLERGIC LUNG will be given in the afternoon. Evening panels, from 8 to 10 p.m. will be devoted to "The Steroid Hormones" and a Pediatric Panel.

Tuesday morning, April 6, there will be nine lectures on THE ALLERGIC SKIN. Dr. Alvan Barach, guest speaker at the luncheon, will talk on "Recent Advances in Inhalational Therapy of Lung Disorders." Eight lectures on MISCELLANEOUS ALLERGIC DISORDERS will be given in the afternoon. Evening panels will be on "Antihistaminic Agents" and "Mold Allergy."

Wednesday morning, April 7, the subject will be THE ALLERGIC PATIENT. Lectures on THE ALLERGIC STATE will be given in the afternoon, and the evening session will have two panels—"Any Questions?" and "Psychosomatic Allergy."

It is also possible that there will be seminars of the Psychosomatic Committee on Tuesday and Wednesday nights running concurrently with other meetings.

From Monday through Friday, April 5-9, from 9:00 a.m. to 5:00 p.m., Dr. Stephen D. Lockey and associates will give lectures and demonstrations on OFFICE AND LABORATORY PROCEDURES.

The *Decennial Congress* begins Thursday morning, April 8, with the full day devoted to a General Session. A Dermatologic Section will be held Friday evening, April 9. Also on Friday, Dr. John Gillaspie, Chairman, will introduce President Peshkin and the guest speaker, Dr. John W. Gowan, Professor of Genetics, Iowa State College of Agriculture and Mechanic Arts, Ames, Iowa, whose subject will be "Individuality as a Factor in Resistance to Disease." Round Table Luncheons are planned for Thursday and Friday. Saturday morning, April 10, there will be a Section on Otolaryngology.

As many as possible will be accommodated in the Roney Plaza Hotel, with the overflow being assigned to adjoining hotels, accessible to the Roney Plaza and immediately adjacent to the Roney Plaza Hotel grounds. The "overflow" guests actually need walk only a few feet along the ocean walk and are as near to the main meeting room in the Roney Plaza as those housed in that hotel. **Please read the Application Form and Register at Once.**

The deadline for papers for the Scientific Session is December 1, 1953. Please submit your papers to Dr. Giles Koelsche, Mayo Clinic, Rochester, Minnesota, before that time.

For detailed information, address the Secretary-Treasurer, ACA, 401 La-Salle Building, Minneapolis 2, Minnesota.

PHILADELPHIA ALLERGY SOCIETY

The Fall Meeting of the Philadelphia Allergy Society is to be held on October 28, at the College of Physicians, Philadelphia.

Dr. Oscar Swineford, Jr., Clinical Professor of Medicine, University of Virginia Medical School, will speak on "Background Observations on the Bacterial Allergy Problem."

A panel discussion will follow on Bacterial Allergy.

"Asthma"—Dr. Oscar Swineford, Jr.
"Allergic Rhinitis"—Dr. Harry P. Schenck
"Bacterial Antigens"—Dr. Joseph Smolens

Two original papers on Allergy will be presented by Dr. David Myers and Dr. Alexander Sterling, of Philadelphia.

Dr. Edmund E. Ehrlich, 319 South 15th Street, Philadelphia, is Secretary.

AMERICAN COLLEGE OF PHYSICIANS COURSE

The American College of Physicians will conduct a course at the University of Pittsburgh, School of Medicine in "Diseases Due to Allergy and Immune Mechanisms," for the week beginning Monday, May 17, 1954. This advanced course will be for physicians already engaged in the practice of allergy. It will consist of didactic presentations, laboratory demonstrations and panel discussions in which the registrants will participate. All those interested please address your inquiry at your earliest opportunity to Leo H. Criep, M.D., The Bigelow, Bigelow at Tunnel Streets. Pittsburgh 19, Pennsylvania.

NEW JERSEY ALLERGY SOCIETY

The New Jersey Allergy Society recently elected the following officers for 1953-54: President, Dr. Edward Seidmon, Plainfield; Vice President, Dr. W. B. Nevius, East Orange; Treasurer, Dr. E. J. Luippold, Mountain Lake; Secretary, Dr. Frank L. Rosen, Newark.

At the meeting held October 15 at the Academy of Medicine in Newark, the speaker was Dr. George Piness of Los Angeles. His topic was "Allergy in General Practice."

SOUTHERN MEDICAL ASSOCIATION

There is always an interesting Section on Allergy at the Southern Medical Association meeting. The 1953 meeting was held at Atlanta, Georgia, October 26-29. Mr. C. P. Loranz, 1020 Empire Building, Birmingham 3, Alabama, is Secretary.

PERSONAL ITEMS

Dr. Merle W. Moore, Portland, a former member of the Board of Regents of the College, is now in charge of the Department of Allergy of the University of Oregon Medical School.

* * *

Dr. John B. Miale, formerly associated with the Marshfield Clinic, Marshfield, Wisconsin, is now Professor of Clinical Pathology of the University of Miami Medical School, and is located at the Jackson Memorial Hospital, Miami, Florida.

BOOK REVIEWS

NUTRITION AND DIET IN ALLERGY. C. S. Bucher, M.D., Champaign, Ill. 528 pages. St. Louis: Educational Publishers, 1953. Price $7.50.

This book, containing more than 1100 recipes is written for the allergic person but should be of use to dietitians and members of the medical profession as well. It gives a wide range of food values, methods of figuring the requirements for an infant, including modifications of cow's milk, goat's milk, soybeans, other vegetable foods and amino-acids, and additions to the formula, carrying the infant through his first year. The young and the older child's nutrition and diet are covered by recipes, menus, and analysis, followed by an explanation giving reasons for certain foods used to obtain a balanced diet. This is important where foods are eliminated for allergenic reasons. There are 1122 recipes in the adult section arranged in milk-free, egg-free, milk and egg-free, wheat-free, wheat and milk-free, wheat and egg-free, wheat, egg and milk-free groups. Each group is further subdivided into appetizers, salads, main dishes, pastries, breads, cakes, desserts, dressings; etc. completing the meal. Sources of certain elements of foods are given, such as eggs, milk, chocolate, cottonseed; etc. Another section gives the calories of a large list of foods in one-fourth pound, one pound and 100 gram quantities.

Unfortunately, yeast is not mentioned as an allergy *per se*. It is listed only under wheat foods which contain wheat as an allergen and suggests one yeast which is free of wheat. Yeasts are important allergens both because of ingestion and probably also because of inhalation. According to Feinberg, ". . . next to *alternaria* the yeasts give the most frequent reactions among the fungi. . . . Allergy to yeast occurs quite frequently and it is important to employ it in routine testing for allergy." There are a number of clinical reports by well known allergists reporting clinical allergy due to yeast. Beer, which is a frequent cause of allergic symptoms, contains malt and yeast which are both frequent offenders.

Considering the 528 pages, the price is reasonable. There is a great need for an up-to-date book on the subject and this is a book which the allergist should not hesitate to recommend to his patients.

THE NATURE AND SIGNIFICANCE OF THE ANTIBODY RESPONSE. Symposium held at the New York Academy of Medicine, March 21 and 22, 1951. Edited by A. M. Pappenheimer, Jr., New York: Columbia University Press, 1953. 227 pages. Price $5.00.

The New York Academy of Medicine has rendered a considerable service in publishing this symposium. It contains authoritative presentations of many of the most important aspects of immunology. In fact, it closely approaches a co-ordinated textbook on this discipline and certainly is more comprehensive, more reliable and more up to date in most of the subjects covered than anything presently available in this language. Its value is further enhanced by the references attached to each paper. The chapters on skin sensitizing antibodies and on reactions mediated by cells are of particular interest for the allergists. The following enumeration of the content will serve to bring out the scope of the book:

(1) Theories of antibody formation, by F. Haurowitz; (2) Sites of antibody formation, by P. D. McMaster; (3) Response of immunized animals to specific and nonspecific stimuli, by J. Freund; (4) Factors affecting the antibody response, by G. Edsall; (5) Persistence of antibodies in man after immunization, by M. Heidelberger; (6) Unity and diversity of antibodies, by E. A. Kabat; (7) Valence

of antibodies, by A. M. Pappenheimer, Jr.; (8) Experimental production of skin-sensitizing antibodies, by W. B. Sherman; (9) Skin-sensitizing antibody and allergy and resistance to insulin, by F. C. Lowell; (10) Immunological reactions mediated by cells, by M. W. Chase; (11) Fate of I^{131}-labeled bovine gamma globulin in rabbits, by F. J. Dixon et al; (12) Fate and effects of injected protein antigens, by C. A. Janeway; (13) The localization of antigen in tissue cells by means of fluorescein-labeled antibody, by A. H. Coons; (14) Radioactive tracers in the study of anti-tissue antibody, by D. Pressman.

This volume will be of great value not only to the worker active in the exploration of immunological phenomena, but also to those who are interested in a better understanding of the theoretical aspects of their daily endeavors.

A.J.W.

THE EPIDEMIOLOGY OF HEALTH. A New York Academy of Medicine Book. Iago Galdston, Editor. New York & Minneapolis: Health Education Council, 1953. 193 pp. Price $4.00.

The book is based on the Eleventh Annual Eastern States Health Education Conference. "Good health is not merely the absence of disease; it implies a sense of well-being" (WHO definition of health). Thus health may be considered as an ecological (in the widest sense of this term) phenomenon, which may be treated for whole populations as is the absence of health—disease—in epidemiology. Hence the title of the symposium. This history of the problem, prophylaxis of disease, infectious or otherwise, nutritional, geriatric, psychiatric, industrial and military health questions are discussed most illustratively by fourteen authoritative speakers. That the common and world-wide problem of health is treated as an attainable group goal, is characteristic for our changing approaches to the medical problems: ". . . the practice of medicine . . . has changed much and is now in the throes of further active change. I believe, too, that the greatest factor is the change of medical viewpoint." In this sense, this book is recommended to the attention of every thoughtful physician.

A.J.W.

ACCIDENTAL OVERDOSE OF CHLOR-TRIMETON

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exceedingly fortunate that the 200 mg dose of Chlor-Trimeton caused no severe or lasting untoward effects in this instance. From this experience, it is not intended to imply that diligence may be relaxed in the administration of Chlor-Trimeton in the injectable 100 mg/cc form. Care should continue to be exercised to use doses within the limits of those recommended for therapy.

WALTER ZERNICH, M.D.

612 United Building
Akron, Ohio

EDWARD GEORGE TATGE

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carry out his assignments. He had done research work in protein chemistry in the Department of Physiological Chemistry, University of Illinois.

Dr. Tatge was past president of the Chicago Society of Allergy and past president of the North Suburban Branch of the Chicago Medical Society.

Surviving are his widow, Elizabeth James Tatge, five sons—William, John, George, James, Arthur, a daughter, Grace Elizabeth, and his father, Edward William.

Officers and members of the College extend sincere sympathy to the family and friends of our revered colleague.

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